EXHIBIT 1

8475758

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 9, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: *9,463,289*
ISSUE DATE: *October 11, 2016*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

John Burson
Certifying Officer

US009463289B2

(12) **United States Patent**
Walsh et al.

(10) **Patent No.: US 9,463,289 B2**
(45) **Date of Patent: Oct. 11, 2016**

(54) **DOSE COUNTERS FOR INHALERS, INHALERS AND METHODS OF ASSEMBLY THEREOF**

(71) Applicants: **IVAX PHARMACEUTICALS IRELAND**, Utrecht (NL); **NORTON WATERFORD**, Utrecht (NL); **TEVA PHARMACEUTICALS IRELAND**, Utrecht (NL)

(72) Inventors: **Declan Walsh**, County Kilkenny (IE); **Derek Fenlon**, County Wexford (IE); **Simon Kaar**, County Cork (IE); **Jan Geert Hazenberg**, County Kilkenny (IE); **Daniel Buck**, County Waterford (IE); **Paul Clancy**, Waterford (IE); **Robert Charles Uschold**, Leominster, MA (US); **Jeffrey A. Karg**, Hopkinton, MA (US)

(73) Assignees: **IVAX Pharmaceuticals Ireland**, Waterford (IE); **Norton (Waterford) Limited**, Waterford (IE); **Teva Pharmaceuticals Ireland**, Waterford (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/103,324**

(22) Filed: **Dec. 11, 2013**

(65) **Prior Publication Data**

US 2014/0096769 A1 Apr. 10, 2014

Related U.S. Application Data

(62) Division of application No. 13/110,532, filed on May 18, 2011, now Pat. No. 8,978,966.

(60) Provisional application No. 61/345,763, filed on May 18, 2010, provisional application No. 61/417,659, filed on Nov. 29, 2010.

(51) **Int. Cl.**
G06M 1/06 (2006.01)
A61M 11/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 15/0071*** (2014.02); ***A61M 11/00*** (2013.01); ***A61M 15/009*** (2013.01);
(Continued)

(58) **Field of Classification Search**
USPC 235/8, 103; 128/200.23
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,174,890 A 11/1979 Johnson
4,669,838 A 6/1987 Hibbard
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2501726 9/2006
EP 1330280 11/2004
(Continued)

OTHER PUBLICATIONS

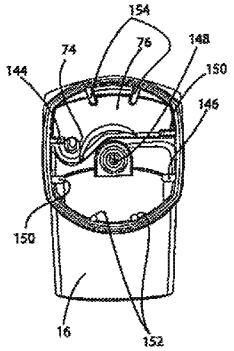
First Examination Report of counterpart New Zealand Patent Application No. 603466, dated Jul. 1, 2013.
(Continued)

Primary Examiner — Daniel Hess
(74) *Attorney, Agent, or Firm* — RatnerPrestia

(57) **ABSTRACT**

A manually operated metered dose inhaler includes a dose counter chamber including a dose display tape driven by a ratchet wheel which is driven in turn by an actuator pawl actuated by movement of a canister, the tape unwinding from a stock bobbin during use of the inhaler, a rotation regulator being provided for the stock bobbin and including a wavelike engagement surface with concavities which engage against control elements in the form of protrusions on resilient forks of a split pin thereby permitting incremental unwinding of the stock bobbin yet resisting excessive rotation if the inhaler is dropped onto a hard surface.

10 Claims, 17 Drawing Sheets



(51) **Int. Cl.**
A61M 15/00 (2006.01)
G06M 1/24 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M15/0025*** (2014.02); ***A61M 15/0026*** (2014.02); ***A61M 15/0065*** (2013.01); ***A61M 15/0078*** (2014.02); ***G06M 1/246*** (2013.01); *A61M 2202/064* (2013.01); *A61M 2205/6063* (2013.01); *A61M 2207/00* (2013.01); *A61M 2207/10* (2013.01); *Y10T 29/49* (2015.01); *Y10T 29/49764* (2015.01); *Y10T 29/49826* (2015.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,687,359	A	8/1987	Barrus	
5,482,030	A	1/1996	Klein	
5,861,911	A	1/1999	Oosaka	
6,446,627	B1	9/2002	Bowman et al.	
6,718,972	B2	4/2004	O'Leary	
8,418,690	B2	4/2013	Power	
8,474,448	B2	7/2013	Oi	
2002/0047021	A1	4/2002	Blacker et al.	
2002/0078949	A1	6/2002	OLeary	
2002/0078950	A1	6/2002	OLeary	
2003/0209239	A1	11/2003	Rand	
2004/0095746	A1	5/2004	Murphy	
2005/0028815	A1	2/2005	Deaton et al.	
2005/0087191	A1	4/2005	Morton et al.	
2006/0096594	A1	5/2006	Bonney et al.	
2006/0107949	A1*	5/2006	Davies et al.	128/200.23
2006/0107979	A1	5/2006	Kim	
2007/0062518	A1	3/2007	Geser	
2008/0242465	A1	10/2008	Strobel	
2009/0178678	A1	7/2009	O'Leary	
2010/0089395	A1	4/2010	Power	
2010/0218759	A1	9/2010	Anderson et al.	
2011/0041845	A1	2/2011	Solomon	
2012/0006322	A1	1/2012	Anderson	

FOREIGN PATENT DOCUMENTS

EP	1486227	12/2004
GB	2320489 A	6/1998
JP	02502129	7/1990
JP	450059	8/1992
JP	07100205	4/1995
JP	10504220	4/1998
JP	2002528144	9/2002
JP	2004501685	1/2004
JP	2008094103	4/2008
JP	2008261423	10/2008
JP	2009233308	10/2009
JP	2009257392	11/2009
JP	2010096308	4/2010
WO	8909078	10/1989
WO	9628205	9/1996
WO	WO 9828033	7/1998
WO	9936115	7/1999
WO	03101514	12/2003
WO	2005102430	11/2005
WO	WO 2006/062449	6/2006
WO	2007012861	2/2007
WO	2007062518	6/2007
WO	WO 2008/023019	2/2008
WO	WO 2008119552	10/2008
WO	2011012325	2/2011
WO	2011012327	2/2011

OTHER PUBLICATIONS

Entire patent prosecution history of U.S. Appl. No. 14/699,567, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler and Method for Counting Doses."
Entire patent prosecution history of U.S. Appl. No. 14/699,578, filed, Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having a Bore and Shaft Arrangement."
Entire patent prosecution history of U.S. Appl. No., 14/699,584, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having an Anti-Reverse Rotation Actuator."
Entire patent prosecution history of U.S. Appl. No. 14/713,612, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/713,620, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/713,633, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/713,643, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 13/110,532, filed May 18, 2011, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,343, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,353, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,363, filed Dec. 1, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,392, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 211.8.
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 212.6.

* cited by examiner

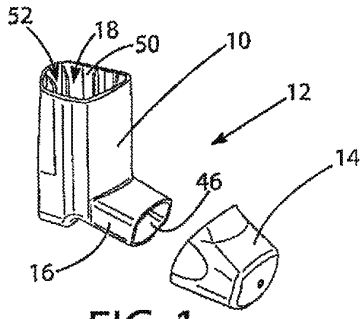


FIG. 1

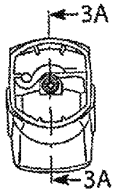


FIG. 2

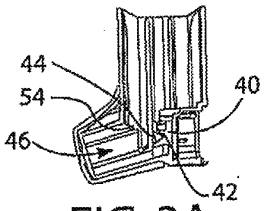


FIG. 3A

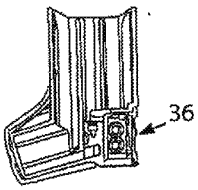


FIG. 3B

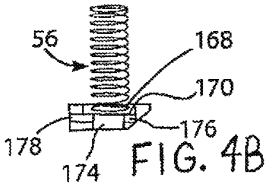


FIG. 4B

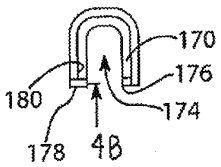


FIG. 4C

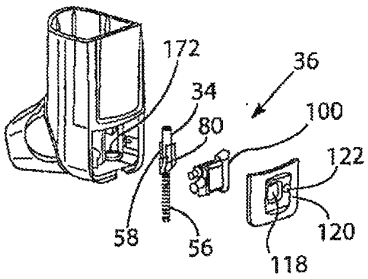


FIG. 4A

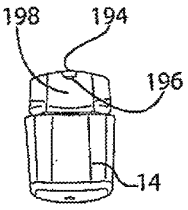


FIG. 5

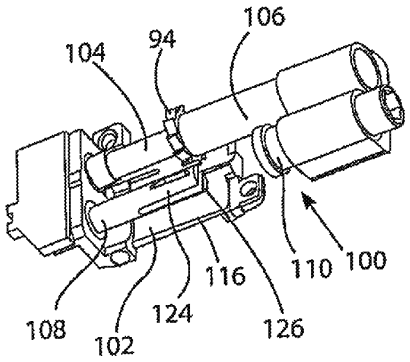


FIG. 6A

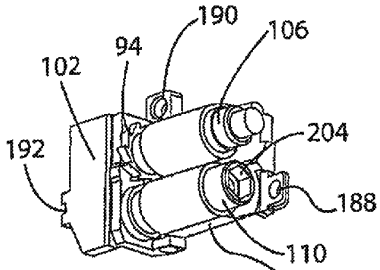


FIG. 6B

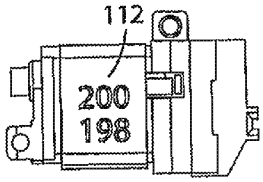


FIG. 6C

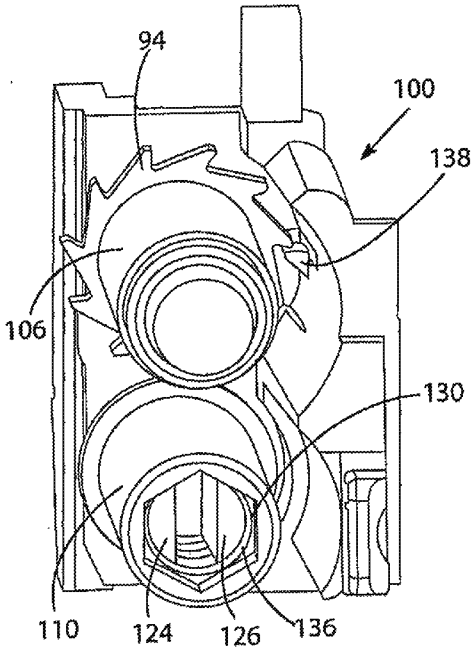


FIG. 6D

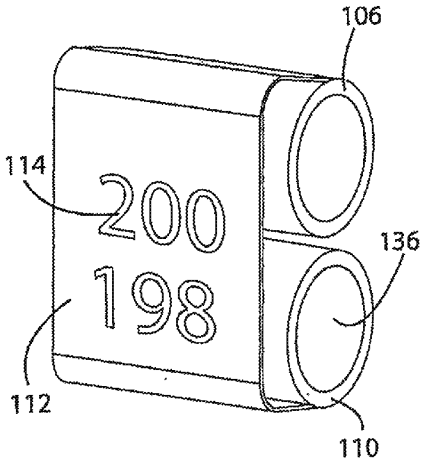


FIG. 6E

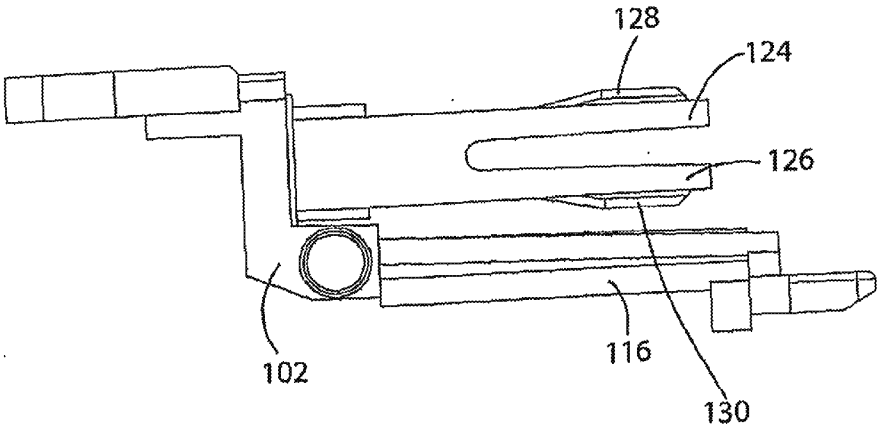


FIG. 6F

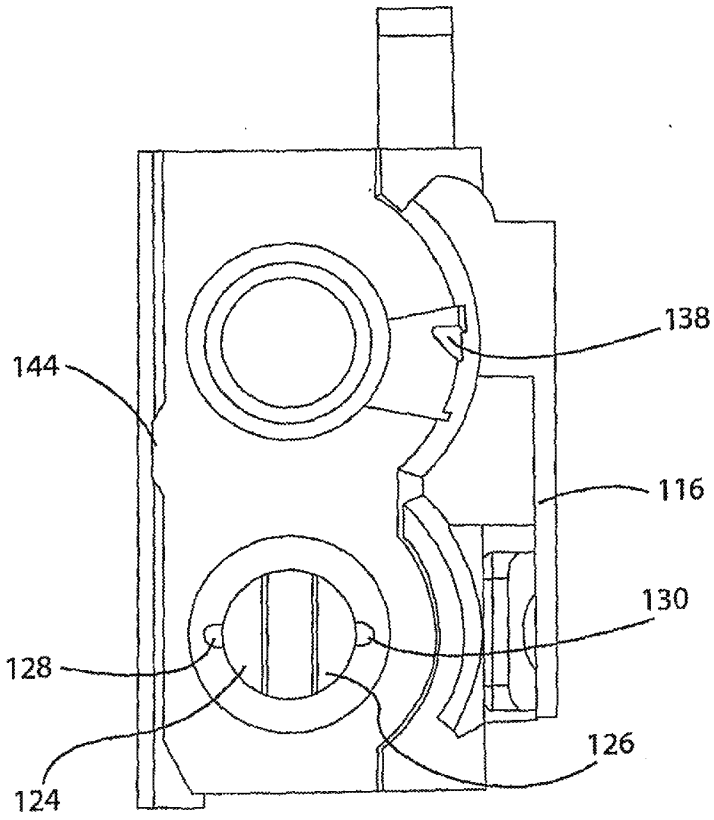


FIG. 6G

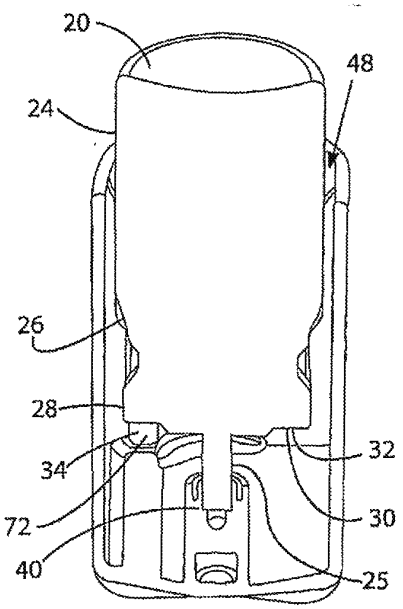


FIG. 7A

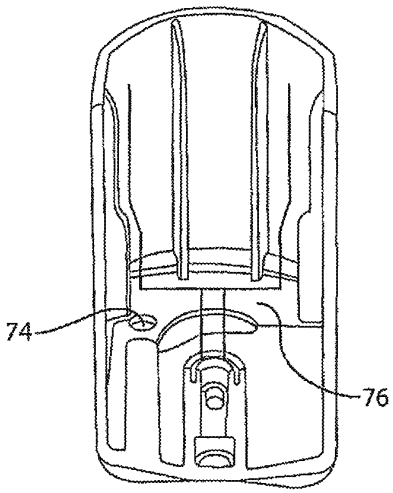


FIG. 7B

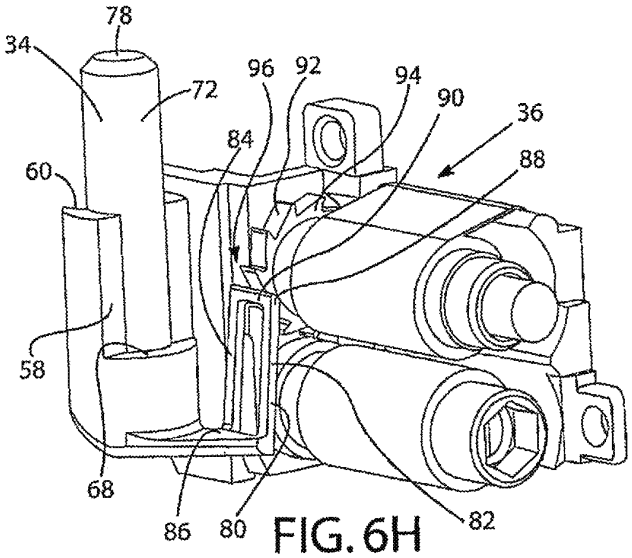


FIG. 6H

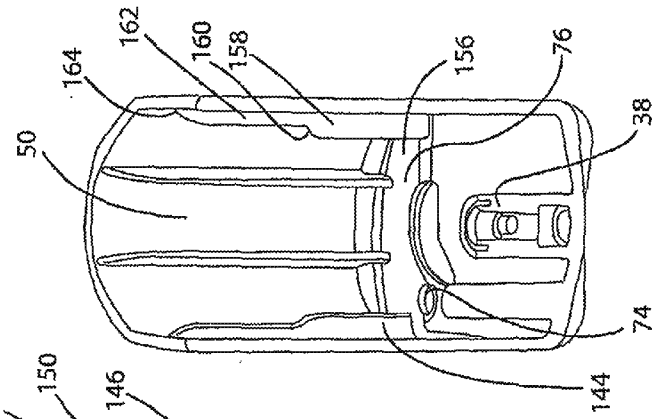


FIG. 7C

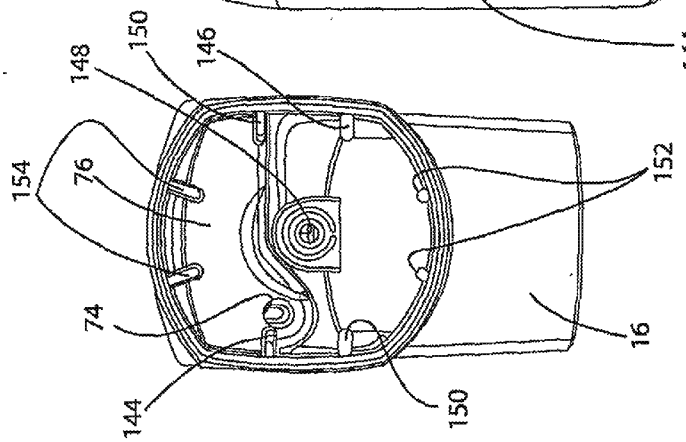


FIG. 7D

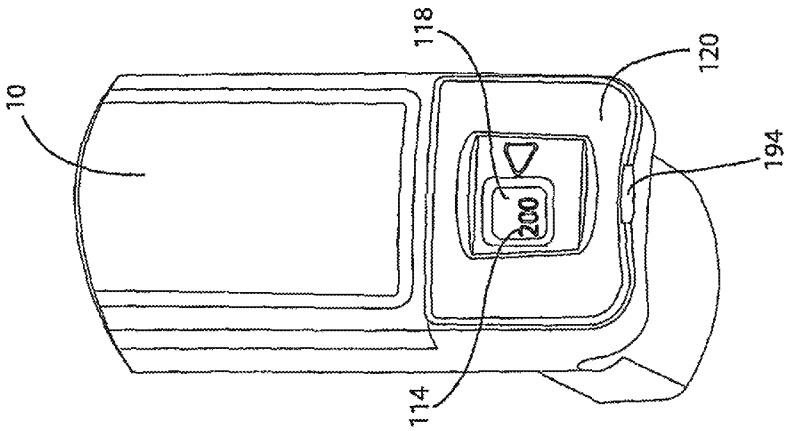


FIG. 8D

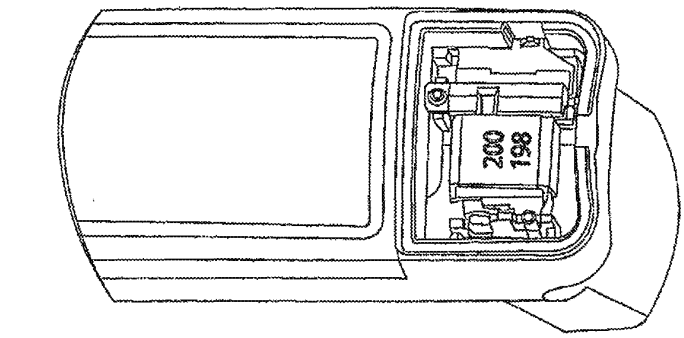


FIG. 8C

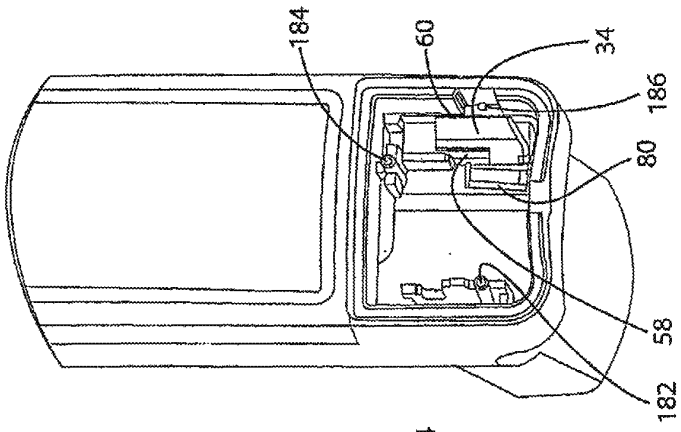


FIG. 8B

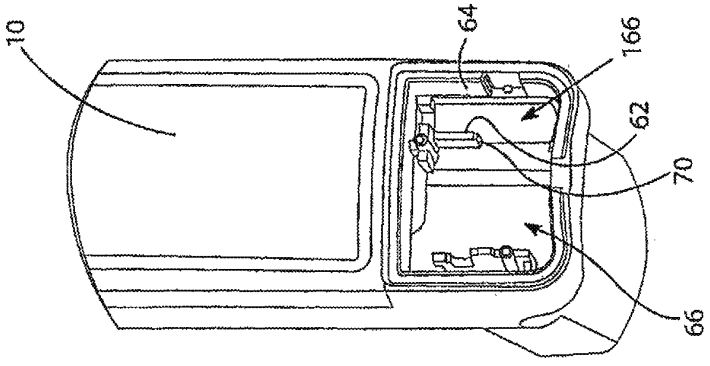


FIG. 8A

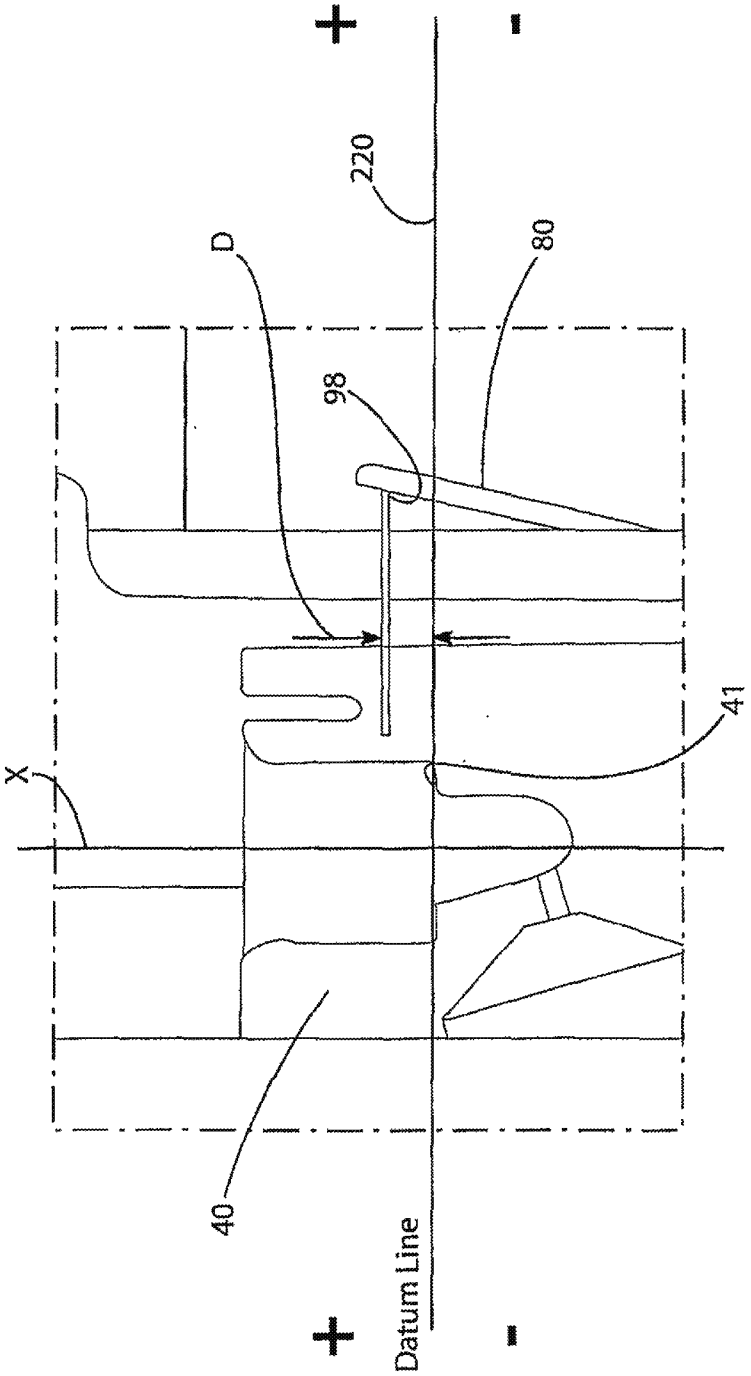


FIG. 9

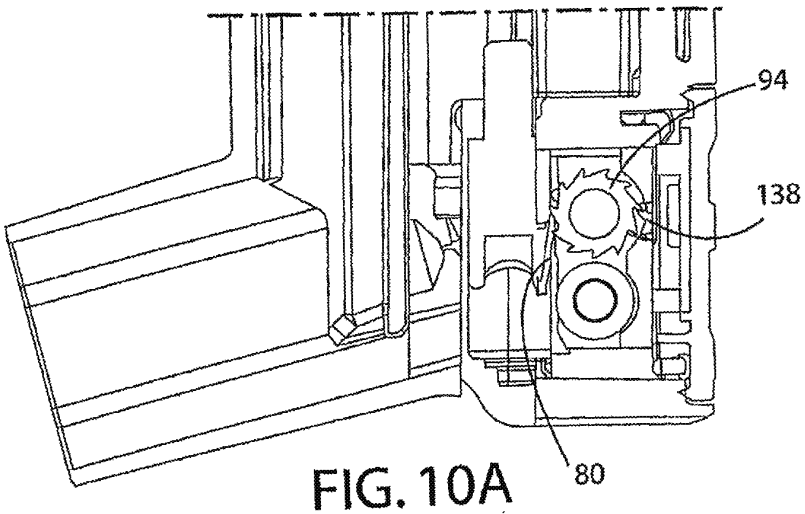


FIG. 10A

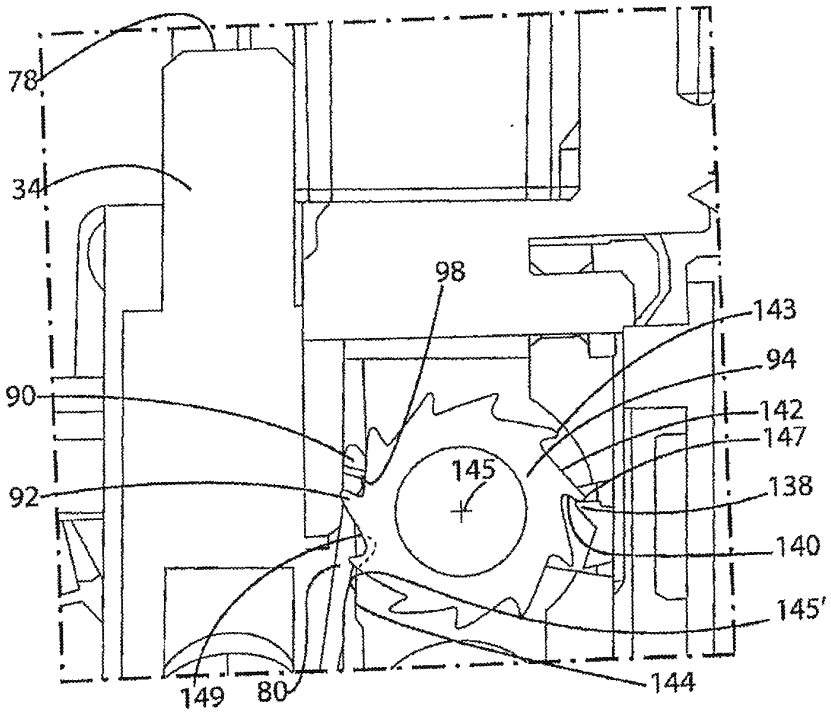


FIG. 10B

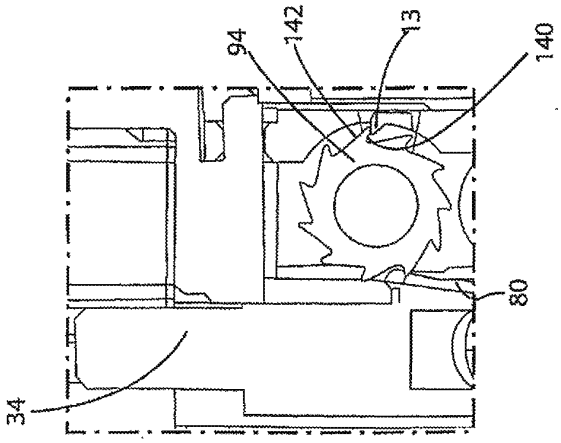


FIG. 10E

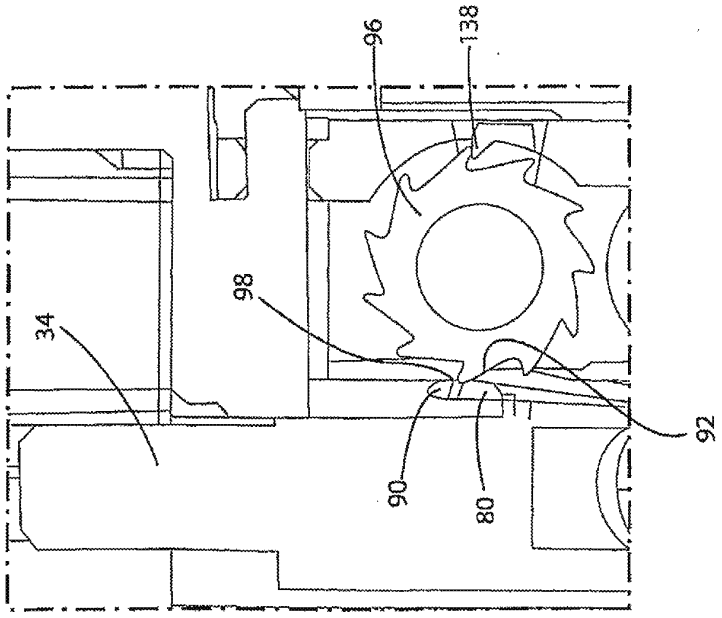


FIG. 10C

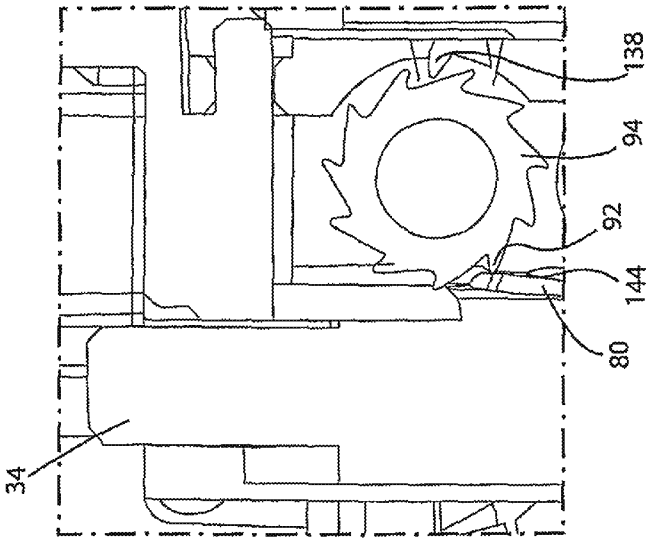


FIG. 10F

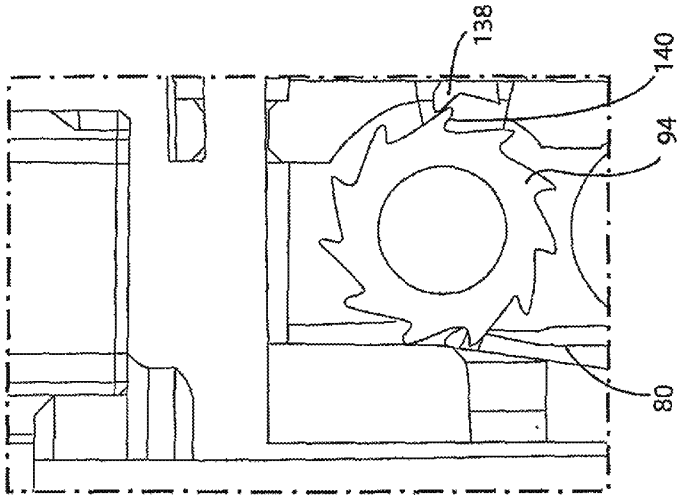


FIG. 10D

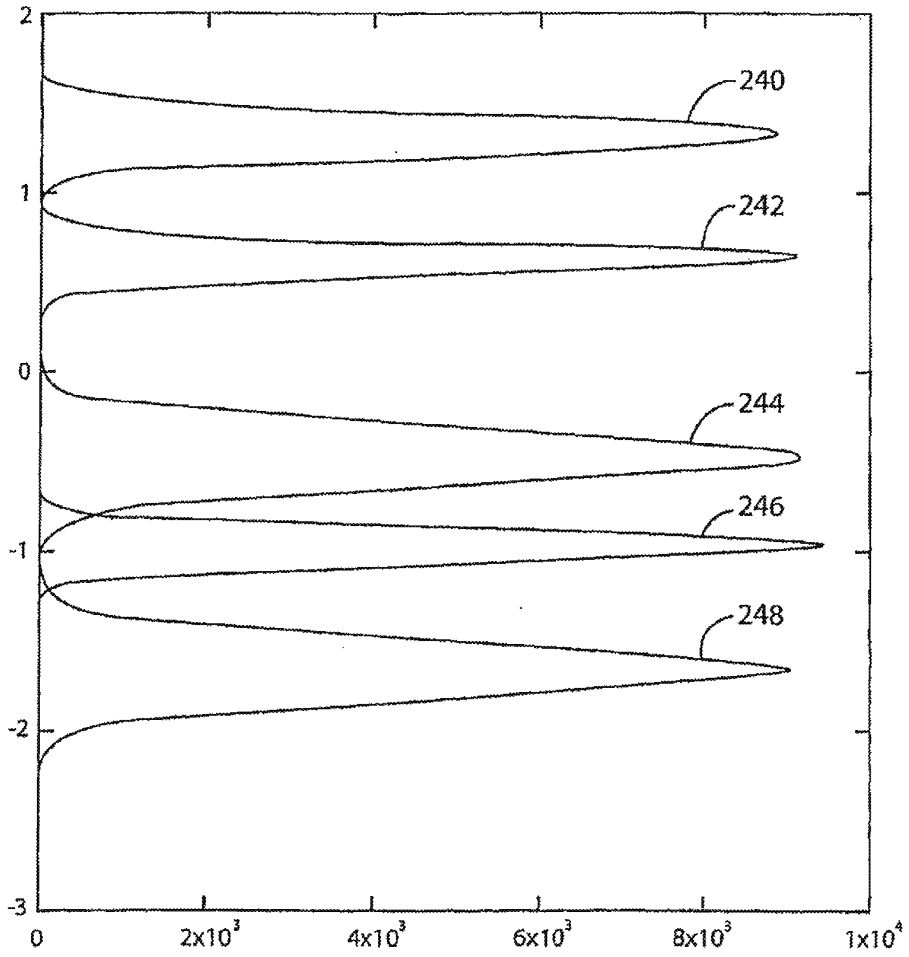

2
1
0
-1
-2
-3
240
242
244
246
248
0
2x10^3
4x10^3
6x10^3
8x10^3
1x10^4

FIG. 11

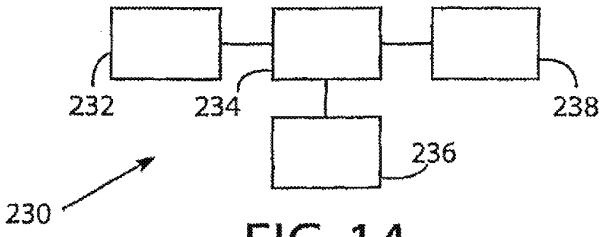

232
234
238
236
230

FIG. 14

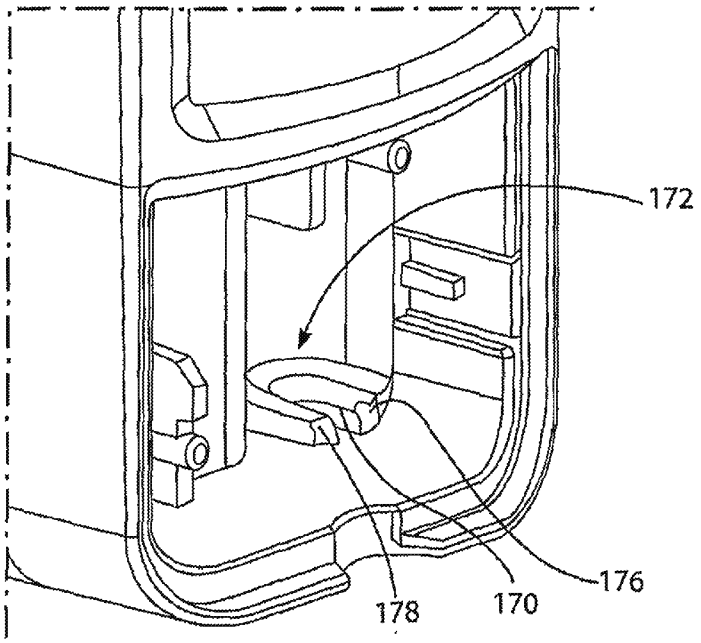
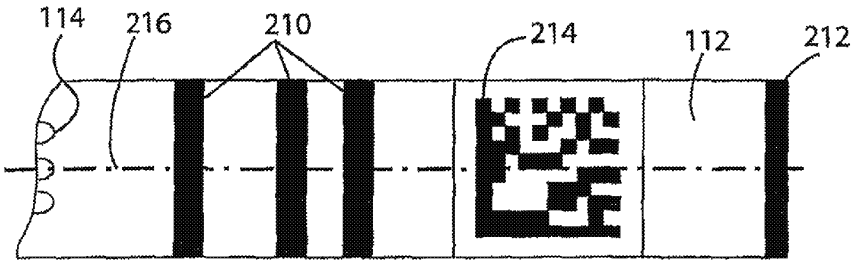


FIG. 12



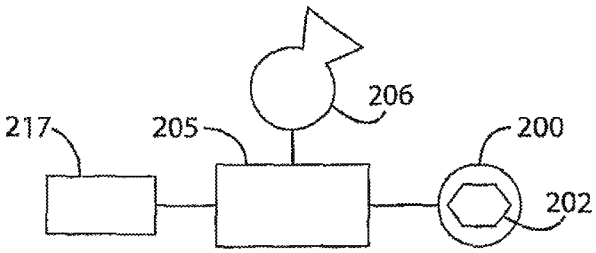


FIG. 13

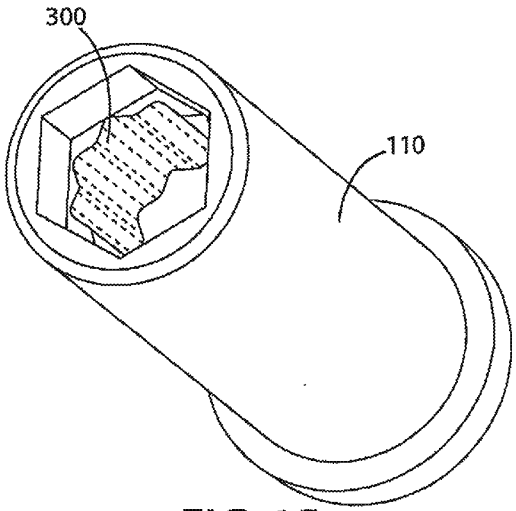


FIG. 15

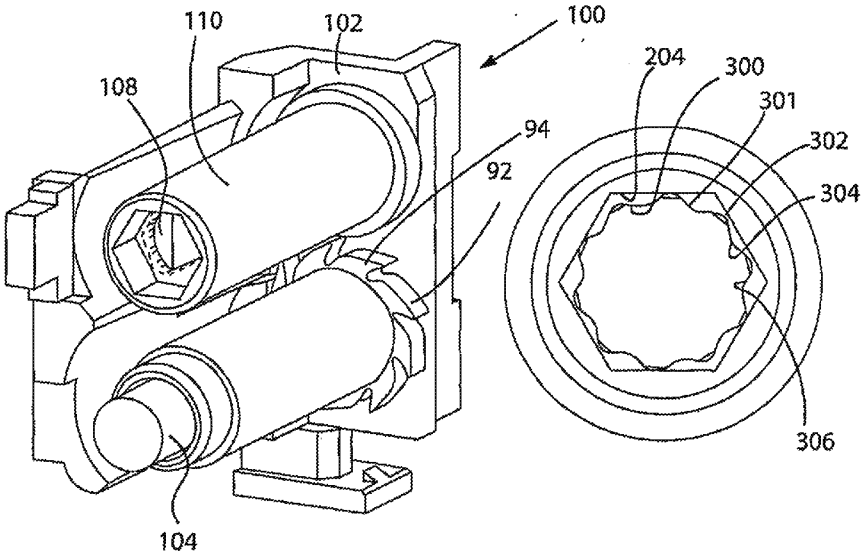


FIG. 20

FIG. 16

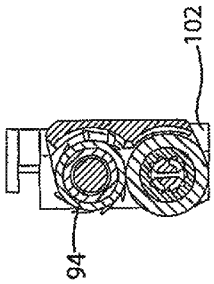


FIG. 19A

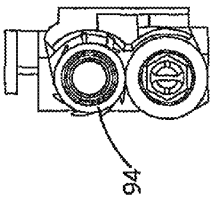


FIG. 19B

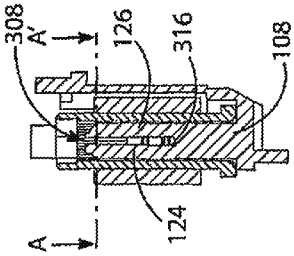


FIG. 19C

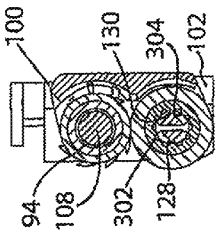


FIG. 18A

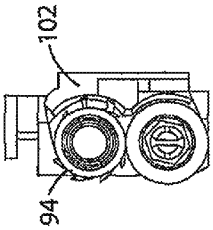


FIG. 18B

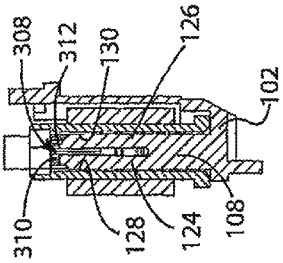


FIG. 18C

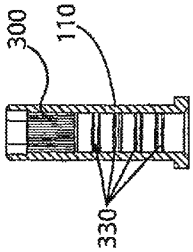


FIG. 17

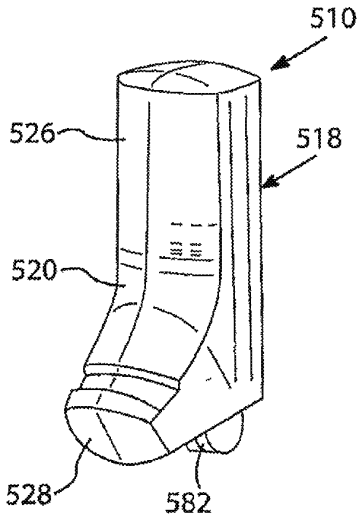

510
526
518
520
528
582

FIG. 21

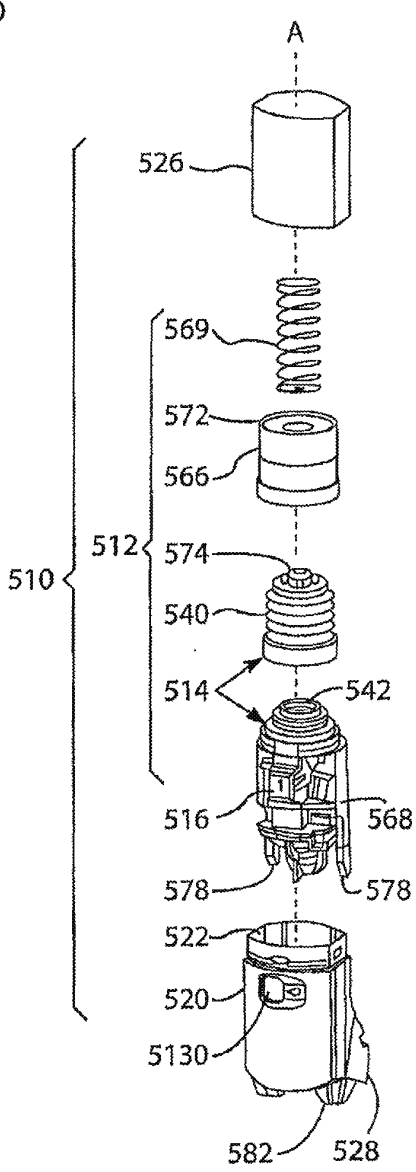

A
526
569
572
566
512
574
510
540
514
542
516
568
578
578
522
520
5130
582
528

FIG. 22

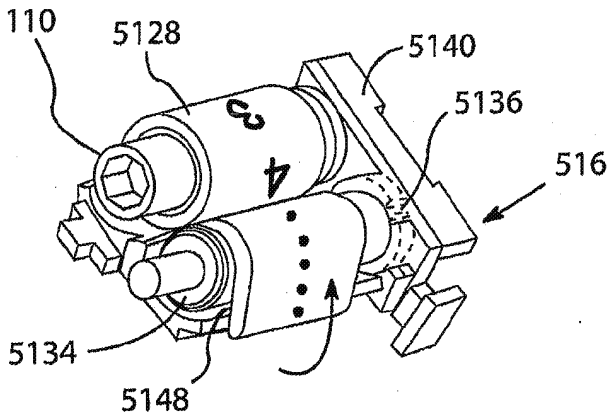

110
5128
5140
5136
516
5134
5148

FIG. 23

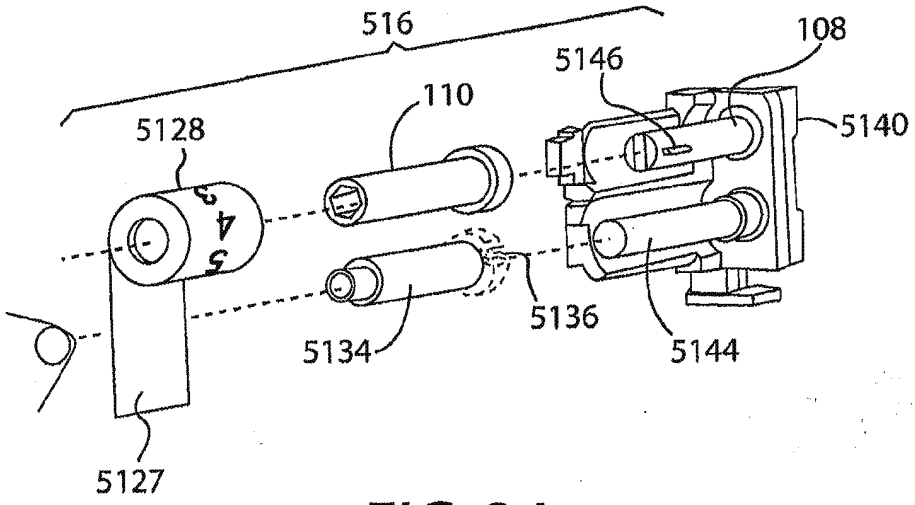

516
108
5146
110
5128
5140
5134
5136
5144
5127

FIG. 24

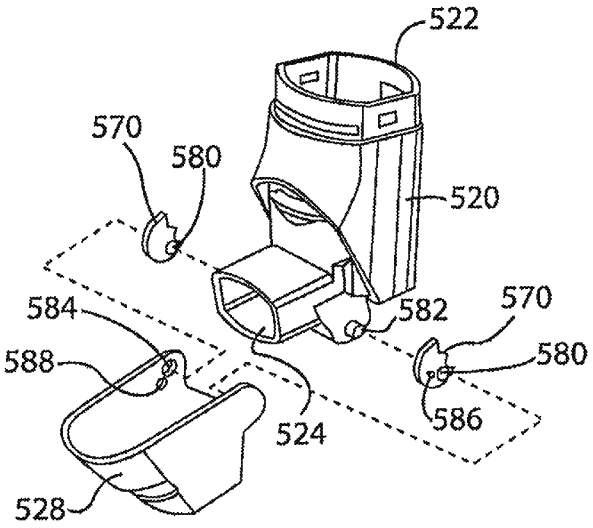


FIG. 25

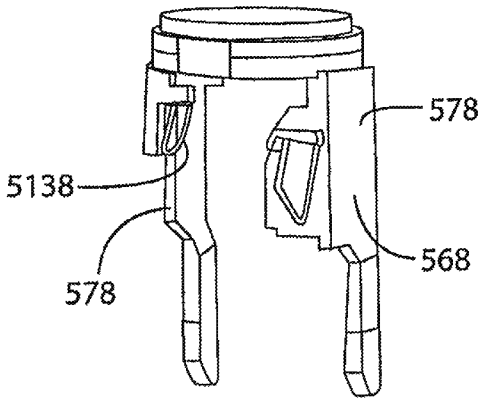


FIG. 26

DOSE COUNTERS FOR INHALERS, INHALERS AND METHODS OF ASSEMBLY THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a divisional patent application of U.S. Non-Provisional patent application Ser. No. 13/110,532, filed May 18, 2011, which claims priority to U.S. Provisional Patent Application No. 61/345,763, filed May 18, 2010, and U.S. Provisional Patent Application No. 61/417,659, filed Nov. 29, 2010, each of which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

The present invention relates to dose counters for inhalers, inhalers and methods of assembly thereof. The invention is particularly applicable to metered dose inhalers including dry power medicament inhalers, breath actuated inhalers and manually operated metered dose medicament inhalers.

BACKGROUND OF THE INVENTION

Metered dose inhalers can comprise a medicament-containing pressurised canister containing a mixture of active drug and propellant. Such canisters are usually formed from a deep-dawn aluminium cup having a crimped lid which carries a metering valve assembly. The metering valve assembly is provided with a protruding valve stem which, in use is inserted as a push fit into a stem block in an actuator body of an inhaler having a drug delivery outlet. In order to actuate a manually operable inhaler, the user applies by hand a compressive force to a closed end of the canister and the internal components of the metering valve assembly are spring loaded so that a compressive force of approximately 15 to 30N is required to activate the device in some typical circumstances.

In response to this compressive force the canister moves axially with respect to the valve stem and the axial movement is sufficient to actuate the metering valve and cause a metered quantity of the drug and the propellant to be expelled through the valve stem. This is then released into a mouthpiece of the inhaler via a nozzle in the stem block, such that a user inhaling through the outlet of the inhaler will receive a dose of the drug.

A drawback of self-administration from an inhaler is that it is difficult to determine how much active drug and/or propellant are left in the inhaler, if any, especially of the active drug and this is potentially hazardous for the user since dosing becomes unreliable and backup devices not always available.

Inhalers incorporating dose counters have therefore become known.

WO 98/280733 discloses an inhaler having a ratchet mechanism for driving a tape drive dose counter. A shaft onto which tape is wound has a friction clutch or spring for restraining the shaft against reverse rotation.

EP-A-1486227 discloses an inhaler for dry powered medicament having a ratchet mechanism for a tape dose counter which is operated when a mouthpiece of the inhaler is closed. Due to the way in which the mouthpiece is opened and closed, and actuation pawl of the device which is mounted on a yoke, travels a known long stroke of consistent length as the mouthpiece is opened and closed.

WO 2008/119552 discloses a metered-dose inhaler which is suitable for breath-operated applications and operates with a known and constant canister stroke length of 3.04 mm+/−0.255 mm. A stock bobbin of the counter, from which a tape is unwound, rotates on a shaft having a split pin intended to hold the stock bobbin taut. However, some dose counters do not keep a particularly reliable count, such as if they are dropped onto a hard surface.

More recently, it has become desirable to improve dose counters further and, in particular, it is felt that it would be useful to provide extremely accurate dose counters for manually-operated canister-type metered dose inhalers. Unfortunately, in these inhalers, it has been found in the course of making the present invention that the stroke length of the canister is to a very large extent controlled on each dose operation by the user, and by hand. Therefore, the stroke length is highly variable and it is found to be extremely difficult to provide a highly reliable dose counter for these applications. The dose counter must not count a dose when the canister has not fired since this might wrongly indicate to the user that a dose has been applied and if done repeatedly the user would throw away the canister or whole device before it is really time to change the device due to the active drug and propellant reaching a set minimum. Additionally, the canister must not fire without the dose counter counting because the user may then apply another dose thinking that the canister has not fired, and if this is done repeatedly the active drug and/or propellant may run out while the user thinks the device is still suitable for use according to the counter. It has also been found to be fairly difficult to assembly some known inhaler devices and the dose counters therefor. Additionally, it is felt desirable to improve upon inhalers by making them easily usable after they have been washed with water.

The present invention aims to alleviate at least to a certain extent one or more of the problems of the prior art.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a counter display arranged to indicate dosage information, a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

The regulator is advantageous in that it helps prevent unwanted motion of the counter display if the counter is dropped.

According to a further aspect of the present invention, the regulator provides a resistance force of greater than 0.1 N against movement of the counter display. According to still a further aspect of the present invention, the resistance force is greater than 0.3 N. According to yet a further aspect of the present invention, the resistance force is from 0.3 to 0.4 N.

Preferably, the counter comprises a tape.

Preferably, the tape has dose counter indicia displayed thereon. The first station may comprise a region of the dose counter where tape is held which is located before a display location, such as a display window, for the counter indicia.

The first station may comprise a first shaft, the tape being arranged on the first shaft and to unwind therefrom upon movement of the counter display.

The first shaft may be mounted for rotation relative to a substantially rotationally fixed element of the dose counter.

The regulator may comprise at least one projection which is arranged on one of the first shaft and the substantially rotationally fixed element and to engage incrementally with one or more formations on the other of the first shaft and the substantially rotationally fixed element.

At least two said projections may be provided. Exactly two said projections maybe provided.

Each projection may comprise a radiused surface.

The at least one projection may be located on the substantially fixed element which may comprise a fixed shaft which is fixed to a main body of the dose counter, the first shaft being rotationally mounted to the fixed shaft.

Preferably, the fixed shaft has at least two resiliently flexible legs (or forks). Each leg may have at least one said projection formed in an outwardly facing direction thereon, said one or more formations being formed on an inwardly facing engagement surface of the first shaft, said at least one projection being arranged to resiliently engage said one or more formations. Preferably, a series of said formations are provided. An even number of said formations may be provided. Eight to twelve of said formations may be provided. In one embodiment, ten said formations are provided.

Each said formation may comprise a concavity formed on an engagement surface. Each concavity may comprise a radiused surface wall portion which preferably merges on at least one side thereof into a flat wall portion surface. The engagement surface may include a series of said concavities, and convex wall portions of the engagement surface may be formed between each adjacent two said concavities, each said convex wall portion comprising a convex radiused wall portion.

Each convex radiused wall portion of each convex wall portion may be connected by said flat wall portion surfaces to each adjacent concavity.

The fixed shaft may comprise a split pin with fork legs and each projection may be located on a said fork leg.

The first shaft may comprise a substantially hollow bobbin.

Said at least one formation may be located on an inner surface of the bobbin. In other embodiments it may be located on an outer surface thereof. Said engagement surface may extend partially along said bobbin, a remainder of the respective inner or outer surface having a generally smooth journal portion along at least a portion thereof.

The drive system may comprise a tooth ratchet wheel arranged to act upon a second shaft which is located at the second station, the second shaft being rotatable to wind the tape onto the second shaft.

The second shaft may be located on a main body of the dose counter spaced from and parallel to the first shaft.

The ratchet wheel may be fixed to the second shaft is arranged to rotate therewith. The ratchet wheel may be secured to an end of the second shaft and aligned coaxially with the second shaft.

The dose counter may include anti-back drive system which is arranged to restrict motion of the second shaft. The anti-back drive system may include a substantially fixed tooth arranged to act upon teeth of the ratchet wheel.

According to a further aspect of the present invention, a dose counter includes an anti-back drive system which is arranged to restrict motion of the second shaft in a tape winding direction.

According to a further aspect of the present invention there is provided a shaft for holding counter tape in a dose counter for an inhaler, the shaft having an engagement surface including incrementally spaced formations located around a periphery thereof, the formations comprising a series of curved concavities and convex portions.

The shaft may comprise a hollow bobbin.

The engagement surface may be a generally cylindrical inwardly directed surface.

The engagement surface may include a flat surface wall portion joining each concavity and convex wall portion.

Each concavity may comprise a radiused wall portion.

Each convex wall portion may comprise a radiused wall portion.

Said concavities may be regularly spaced around a longitudinal axis of the shaft.

Said convex wall portions may be regularly spaced around a longitudinal axis of the shaft.

In some embodiments there may be from eight to twelve said concavities and/or concavities regularly spaced around a longitudinal axis thereof.

One embodiment includes ten said concavities and/or convex wall portions regularly spaced around a longitudinal axis of the shaft.

According to a further aspect of the present invention there is provided a shaft and counter tape assembly for use in a dose counter for an inhaler, the assembly comprising a rotatable shaft and a counter tape which is wound around the shaft and is adapted to unwind therefrom upon inhaler actuation, the shaft having an engagement surface which includes incrementally spaced formations located around a periphery thereof.

According to a further aspect of the present invention there is provided an inhaler for the inhalation of medication and the like, the inhaler including a dose counter as in the first aspect of the present invention.

A preferred construction consists of a manually operated metered dose inhaler including a dose counter chamber including a dose display tape driven by a ratchet wheel which is driven in turn by an actuator pawl actuated by movement of a canister, the tape unwinding from a stock bobbin during use of the inhaler, a rotation regulator being provided for the stock bobbin and comprising a wavelike engagement surface with concavities which engage against control elements in the form of protrusions on resilient forks of a split pin thereby permitting incremental unwinding of the stock bobbin yet resisting excessive rotation if the inhaler is dropped onto a hard surface.

According to another aspect of the present invention there is provided a dose counter for a metered dose inhaler having a body arranged to retain a medicament canister of predetermined configuration for movement of the canister relative thereto; the dose counter comprising: an incremental counting system for counting doses, the incremental counting system having a main body, an actuator arranged to be driven in response to canister motion and to drive an incremental output member in response to canister motion, the actuator and incremental output member being configured to have predetermined canister fire and count configurations in a canister fire sequence, the canister fire configuration being determined by a position of the actuator relative to a datum at which the canister fires medicament and the count configuration being determined by a position of the actuator relative to the datum at which the incremental count system makes an incremental count, wherein the actuator is arranged to reach a position thereof in the count configuration at or after a position thereof in the canister fire configuration.

This arrangement has been found to be highly advantageous since it provides an extremely accurate dose counter

which is suitable for use with manually operated metered dose inhalers. It has been found that dose counters with these features have a failure rate of less than 50 failed counts per million full canister activation depressions. It has been found in the course of making the present invention that highly reliable counting can be achieved with the dose counter counting at or soon after the point at which the canister fires. It has been is covered by the present inventors that momentum and motion involved in firing the canister, and in some embodiments a slight reduction in canister back pressure on the user at the time of canister firing, can very reliably result in additional further motion past the count point.

The actuator and incremental counting system may be arranged such that the actuator is displaced less than 1 mm, typically 0.25 to 0.75 mm, more preferably about 0.4 to 0.6 mm, relative to the body between its location in the count and fire configurations, about 0.48 mm being preferred. The canister, which can move substantially in line with the actuator, can reliably move this additional distance so as to achieve very reliable counting.

The incremental count system may comprise a ratchet mechanism and the incremental output member may comprise a ratchet wheel having a plurality of circumferentially spaced teeth arranged to engage the actuator.

The actuator may comprise an actuator pawl arranged to engage on teeth of the ratchet wheel. The actuator pawl may be arranged to be connected to or integral with an actuator pin arranged to engage and be depressed by a medicament canister bottom flange. The actuator pawl may be generally U-shaped having two parallel arms arranged to pull on a central pawl member arranged substantially perpendicular thereto. This provides a very reliable actuator pawl which can reliably pull on the teeth of the ratchet wheel.

The incremental count system may include a tape counter having tape with incremental dose indicia located thereon, the tape being positioned on a tape stock bobbin and being arranged to unwind therefrom.

The actuator and incremental output member may be arranged to provide a start configuration at which the actuator is spaced from the ratchet output member, a reset configuration at which the actuator is brought into engagement with the incremental output member during a canister fire sequence, and an end configuration at which the actuator disengages from the ratchet output during a canister fire sequence.

The actuator may be arranged to be located about 1.5 to 2.0 mm, from its location in the fire configuration, when in the start configuration, about 1.80 mm being preferred.

The actuator may be arranged to be located about 1.0 to 1.2 mm, from its location in the fire configuration, when in the reset configuration, about 1.11 mm being preferred.

The actuator may be arranged to be located about 1.1 to 1.3 mm, from its location in the fire configuration, when in the end configuration, about 1.18 mm being preferred.

These arrangements provide extremely reliable dose counting, especially with manually operated canister type metered dose inhalers.

The main body may include a formation for forcing the actuator to disengage from the incremental output member when the actuator is moved past the end configuration. The formation may comprise a bumped up portion of an otherwise generally straight surface against which the actuator engages and along which it is arranged to slide during a canister firing sequence.

The dose counter may include a counter pawl, the counter pawl having a tooth arranged to engage the incremental output member, the tooth and incremental output member being arranged to permit one way only incremental relative motion therebetween. When the incremental output member comprises a ratchet wheel, the tooth can therefore serve as an anti-back drive tooth for the ratchet wheel, thereby permitting only one way motion or rotation thereof.

The counter pawl may be substantially fixedly mounted on the main body of the incremental count system and the counter pawl may be arranged to be capable of repeatedly engaging equi-spaced teeth of the incremental output member in anti-back drive interlock configurations as the counter is operated. The counter pawl may be positioned so that the incremental output member is halfway, or substantially halfway moved from one anti-back drive interlock configuration to the next when the actuator and incremental output member are in the end configuration thereof. This is highly advantageous in that it minimises the risk of double counting or non-counting by the dose counter.

According to a further aspect of the invention there is provided an inhaler comprising a main body arranged to retain a medicament canister of predetermined configuration and a dose counter mounted in the main body.

The inhaler main body may include a canister receiving portion and a separate counter chamber, the dose counter being located within the main body thereof, the incremental output member and actuator thereof inside the counter chamber, the main body of the inhaler having wall surfaces separating the canister-receiving portion and the counter chamber, the wall surfaces being provided with a communication aperture, an actuation member extending through the communication aperture to transmit canister motion to the actuator.

According to a further aspect of the present invention there is a provided an inhaler for metered dose inhalation, the inhaler comprising a main body having a canister housing arranged to retain a medicament canister for motion therein, and a dose counter, the dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of a medicament canister, wherein the canister housing has an inner wall, and a first inner wall canister support formation located directly adjacent the actuation member.

This is highly advantageous in that the first inner wall canister support formation can prevent a canister from rocking too much relative to the main body of the inhaler. Since the canister may operate the actuation member of the dose counter, this substantially improves dose counting and avoids counter errors.

The canister housing may have a longitudinal axis which passes through a central outlet port thereof, the central outlet port being arranged to mate with an outer canister fire stem of a medicament canister, the inner wall canister support formation, the actuation member and the outlet port lying in a common plane coincident with the longitudinal axis. Accordingly, this construction may prevent the canister from rocking towards the position of the dose counter actuation member, thereby minimising errors in counting.

The canister housing may have a further inner canister wall support formation located on the inner wall opposite, or substantially opposite, the actuation member. Accordingly, the canister may be supported against rocking motion away from the actuator member so as to minimise count errors.

The canister housing may be generally straight and tubular and may have an arrangement in which each said inner wall support formation comprises a rail extending longitudinally along the inner wall.

Each said rail may be stepped, in that it may have a first portion located towards a medicine outlet end or stem block of the canister housing which extends inwardly a first distance from a main surface of the inner wall and a second portion located toward an opposite end of the canister chamber which extends inwardly a second, smaller distance from the main surface of the inner wall. This may therefore enable easy insertion of a canister into the canister housing such that a canister can be lined up gradually in step wise function as it is inserted into the canister housing.

The inhaler may include additional canister support rails which are spaced around an inner periphery of the inner wall of the canister housing and which extend longitudinally therealong.

At least one of the additional rails may extend a constant distance inwardly from the main surface of the inner wall.

At least one of the additional rails may be formed with a similar configuration to the first inner wall canister support formation.

The dose counter may, apart from said at least a portion of the actuation member, be located in a counter chamber separate from the canister housing, the actuation member comprising a pin extending through an aperture in a wall which separates the counter chamber and the canister housing.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicaments having: a body for retaining a medicament store; the body including a dose counter, the dose counter having a moveable actuator and a return spring for the actuator, the return spring having a generally cylindrical and annular end; the body having a support formation therein for supporting said end of the return spring, the support formation comprising a shelf onto which said end is engageable and a recess below the shelf.

This shelf and recess arrangement is highly advantageous since it allows a tool (such as manual or mechanical tweezers) to be used to place the return spring of the actuator onto the shelf with the tool then being withdrawn at least partially via the recess.

The shelf may be U-shaped.

The support formation may include a U-shaped upstanding wall extending around the U-shaped shelf, the shelf and upstanding wall thereby forming a step and riser of a stepped arrangement.

The recess below the shelf my also be U-shaped.

At least one chamfered surface may be provided at an entrance to the shelf. This may assist in inserting the actuator and return spring into position.

A further aspect of the invention provides a method of assembly of an inhaler which includes the step of locating said end of said spring on the shelf with an assembly tool and then withdrawing the assembly tool at least partly via the recess. This assembly method is highly advantageous compared to prior art methods in which spring insertion has been difficult and in which withdrawal of the tool has sometimes accidentally withdrawn the spring again.

The cylindrical and annular end of the spring may be movable in a direction transverse to its cylindrical extent into the shelf while being located thereon.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament, the inhaler having a body for retaining a medicament store; and a dose counter, the dose counter having a moveable actuator and a chassis mounted on the body; the chassis being heat staked in position on the body. This is be highly advantageous in that the chassis can be very accurately positioned and held firmly in place, thereby further improving counting accuracy compared to prior art arrangements in which some movement of the chassis relative to the body may be tolerated in snap-fit connections.

The chassis may have at least one of a pin or aperture heat staked to a respective aperture or pin of the body.

The chassis may have a ratchet counter output member mounted thereon.

The ratchet counter output member may comprise a ratchet wheel arranged to reel in incrementally a dose meter tape having a dosage indicia located thereon.

According to a further aspect of the present invention there is provided a method of assembling an inhaler including the step of heat staking the chassis onto the body. The step of heat staking is highly advantageous in fixedly positioning the chassis onto the body in order to achieve highly accurate dose counting in the assembled inhaler.

The method of assembly may include mounting a spring-returned ratchet actuator in the body before heat staking the chassis in place. The method of assembly may include pre-assembling the chassis with a dose meter tape prior to the step of heat staking the chassis in place. The method of assembly may include attaching a dose meter cover onto the body after the heat staking step. The cover may be welded onto the body or may in some embodiments be glued or otherwise attached in place.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament and having a body, the body have a main part thereof for retaining a medicament store; and a dose counter, the dose counter being located in a dose counter chamber of the body which is separated from the main part of the body, the dose counter chamber of the body having a dosage display and being perforated so as to permit the evaporation of water or aqueous matter in the dose counter chamber into the atmosphere.

This is high advantageous since it enables the inhaler to be thoroughly washed and the dose counting chamber can thereafter dry out fully.

The display may comprise a mechanical counter display inside the dose counter chamber and a window for viewing the mechanical counter display. The mechanical counter display may comprise a tape. The perforated dose counter chamber may therefore enable reliable washing of the inhaler, if desired by the user, and may therefore dry out without the display window misting up.

The dose counter chamber may be perforated by a drain hole formed through an outer hole of the body. The drain hole may be located at a bottom portion of the body of the inhaler, thereby enabling full draining of the inhaler to be encouraged after washing when the inhaler is brought into an upright position.

According to a further aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a display tape arranged to be incrementally driven from a tape stock bobbin onto an incremental tape take-up drive shaft, the bobbin having an internal bore supported by and for rotation about a support shaft, at least one of the bore and support shaft having a protrusion which is resiliently biased into frictional engagement with the other of the bore and support shaft with longitudinally extending mutual frictional interaction. This arrangement may provide good friction for the bobbin, thereby improving tape counter display accuracy and preventing the bobbin from unwinding undesirably for example if the inhaler is accidentally dropped.

The support shaft may be forked and resilient for resiliently biasing the support shaft and bore into frictional engagement.

The support shaft may have two forks, or more in some cases, each having a radially extending protrusion having a friction edge extending therealong parallel to a longitudinal axis of the support shaft for frictionally engaging the bore of the support shaft with longitudinally extending frictional interaction therebetween.

The bore may be a smooth circularly cylindrical or substantially cylindrical bore.

Each of the above inhalers in accordance with aspects of the present invention may have a medicament canister mounted thereto.

The canister may comprise a pressurised metered dose canister having a reciprocally movable stem extending therefrom and movable into a main canister portion thereof for releasing a metered dose of medicament under pressure, for example by operating a metered dose valve inside the canister body. The canister may be operable by pressing by hand on the main canister body.

In cases in which one or more support rails or inner wall support formations are provided, the canister may at all times when within the canister chamber have a clearance of about 0.25 to 0.35 mm from the first inner wall support formation. The clearance may be almost exactly 0.3 mm. This clearance which may apply to the canister body itself or to the canister once a label has been applied, is enough to allow smooth motion of the canister in the inhaler while at the same time preventing substantial rocking of the canister which could result in inaccurate counting by a dose counter of the inhaler, especially when lower face of the canister is arranged to engage an actuator member of the dose counter for counting purposes.

According to a further aspect of the invention, a method of assembling a dose counter for an inhaler comprises the steps of providing a tape with dosing indicia thereon; providing tape positioning indicia on the tape; and stowing the tape while monitoring for the tape positioning indicia with a sensor. The method advantageously permits efficient and accurate stowing of the tape, e.g. by winding.

The dosing indicia may be provided as numbers, the tape positioning indicia may be provided as one or more lines across the tape. The stowing step comprises winding the tape onto a bobbin or shaft, and, optionally, stopping winding when the positioning indicia are in a predetermined position. The tape may be provided with pixelated indicia at a position spaced along the tape from the positioning indicia. The tape may also be provided with a priming dot.

According to a further aspect of the invention, a tape system for a dose counter for an inhaler has a main elongate tape structure, and dosing indicia and tape positioning indicia located on the tape structure. The tape positioning indicia may comprise at least one line extending across the tape structure. The tape system may comprise pixelated indicia located on the tape structure and spaced from the positioning indicia. The tape system may comprise a priming dot located on the tape structure. The positioning indicia may be located between the timing dot and the pixelated indicia. The main elongate tape structure may have at least one end thereof wound on a bobbin or shaft.

A further aspect of the invention provides a method of designing an incremental dose counter for an inhaler comprising the steps of calculating nominal canister fire and dose counter positions for a dose counter actuator of the inhaler; calculating a failure/success rate for dose counters built to tolerance levels for counting each fire of inhalers in which the dose counter actuators may be applied; and selecting a tolerance level to result in said failure/success rate to be at or below/above a predetermined value. This is highly advantageous in that it allows an efficient and accurate prediction of the reliability of a series of inhaler counters made in accordance with the design.

The method of designing may include selecting the failure/success rate as a failure rate of no more than one in 50 million. The method of designing may include setting an average count position for dose counters built to the tolerances to be at or after an average fire position thereof during canister firing motion. The method of designing may include setting the average count position to be about 0.4 to 0.6 mm after the average fire position, such as about 0.48 mm after. The method of designing may include setting tolerances for the standard deviation of the fire position in dose counters built to the tolerances to be about 0.12 to 0.16 mm, such as about 0.141 mm. The method of designing may include setting tolerances for the standard deviation of the count positions in dose counters built to the tolerances to be about 0.07 to 0.09 mm, such as about 0.08 mm. A further aspect of the invention provides a computer implemented method of designing an incremental dose counter for an inhaler which includes the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing in a production run a series of incremental dose counters for inhalers which comprises manufacturing the series of dose counters in accordance with the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing a series of incremental dose counters for inhalers, which comprises manufacturing the dose counters with nominal canister fire and dose count positions of a dose counter actuator relative to a dose counter chassis (or inhaler main body), and which includes building the dose counters with the average dose count position in the series being, in canister fire process, at or after the average canister fire position in the series.

According to a further aspect of the invention, the method provides fitting each dose counter in the series of incremental dose counters to a corresponding main body of an inhaler.

These aspects advantageously provide for the production run of a series of inhalers and dose counters which count reliably in operation.

According to a further aspect of the invention, an incremental dose counter for a metered dose inhaler has a body arranged to retain a canister for movement of the canister relative thereto, the incremental dose counter having a main body, an actuator arranged to be driven and to drive an incremental output member in a count direction in response to canister motion, the actuator being configured to restrict motion of the output member in a direction opposite to the count direction. This advantageously enables an inhaler dose counter to keep a reliable count of remaining doses even if dropped or otherwise jolted.

The output member may comprise a ratchet wheel. The actuator may comprise a pawl and in which the ratchet wheel and pawl are arranged to permit only one-way ratcheting motion of the wheel relative to the pawl. The dose counter may include an anti-back drive member fixed to the main body. In a rest position of the dose counter, the ratchet wheel is capable of adopting a configuration in which a back surface of one tooth thereof engages the anti-back drive member and the pawl is spaced from an adjacent back

surface of another tooth of the ratchet wheel without positive drive/blocking engagement between the pawl and wheel.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention may be carried out in various ways and preferred embodiment of a dose counter, inhaler and methods of assembly, design and manufacture will now be described with reference to the accompanying drawings in which:

FIG. **1** is an isometric view of a main body of an embodiment of an inhaler related to the invention together with a mouthpiece cap therefor;

FIG. **2** is a top plan view of the components as shown in FIG. **1**;

FIG. **3**A is a section on the plane **3**A-**3**A in FIG. **2**;

FIG. **3**B is a view corresponding to FIG. **3**A but with a dose counter fitted to the main body of the inhaler;

FIG. **4**A is an exploded view of the inhaler main body, mouthpiece cap, dose counter and a dose counter window;

FIG. **4**B is a view in the direction **4**B in FIG. **4**C of a spring retainer of the dose counter;

FIG. **4**C is a top view of the spring retainer of FIG. **4**B;

FIG. **5** is a bottom view of the assembled inhaler main body, mouthpiece cap, dose counter and dose counter window;

FIGS. **6**A, **6**B, **6**C, **6**D, **6**E, **6**F, **6**G and **6**H are various views of dose counter components of the inhaler;

FIGS. **7**A and **7**B are sectional views showing canister clearance inside the main body of the inhaler;

FIG. **7**C is a further sectional view similar to that of FIG. **7**B but with the canister removed;

FIG. **7**D is a top plan view of the inhaler main body;

FIGS. **8**A, **8**B, **8**C and **8**D show the inhaler main body and dose counter components during assembly thereof;

FIG. **9** shows a sectional side view of a datum line for an actuator pawl of the dose counter;

FIGS. **10**A, **10**B, **10**C, **10**D, **10**E and **10**F show various side views of positions and configurations of the actuator pawl, a ratchet wheel, and a count pawl;

FIG. **11** shows distributions for tolerances of start, reset, fire, count and end positions for the actuator of the dose counter;

FIG. **12** is an enlarged version of part of FIG. **4**A;

FIG. **13** shows an end portion of a tape of the dose counter;

FIG. **14** shows a computer system for designing the dose counter;

FIG. **15** is an isometric view of a stock bobbin modified in accordance with the present invention for use in the dose counter of the inhaler of FIGS. **1** to **14**;

FIG. **16** shows an end view of the stock bobbin of FIG. **15**;

FIG. **17** is a section through a longitudinal axis of the stock bobbin of FIGS. **15** and **16**;

FIGS. **18**A to **18**C are views of the stock bobbin of FIGS. **15** to **17** mounted in the dose counter chassis of FIGS. **1** to **14**, with the control elements of the forks of the second shaft (or split pin) having a profile slightly different to that in FIG. **6**F, with the forks in a compressed configuration;

FIGS. **19**A to **19**C are views equivalent to FIGS. **18**A to **18**C but with the forks in a more expanded configuration due to a different rotational position of the stock bobbin;

FIG. **20** is an isometric view of the chassis assembled and including the stock bobbin of FIGS. **15** to **17** but excluding the tape for reasons of clarity;

FIG. **21** is a view of a preferred embodiment of a dry powder inhaler in accordance with the present invention;

FIG. **22** is an exploded view of the inhaler of FIG. **21**;

FIG. **23** is a view of a dose counter of the inhaler of FIG. **21**;

FIG. **24** is an exploded view of the dose counter shown in FIG. **23**;

FIG. **25** is an exploded view of parts of the inhaler of FIG. **21**; and

FIG. **26** is a view of a yoke of the inhaler of FIG. **21**.

DETAILED DESCRIPTION OF THE INVENTION

FIG. **1** shows a main body **10** of a manually operated metered dose inhaler **12** in accordance with an embodiment related to the present invention and having a mouthpiece cap **14** securable over a mouthpiece **16** of the main body.

The main body has a canister chamber **18** into which a canister **20** (FIG. **7**A) is slideable. The canister **20** has a generally cylindrical main side wall **24**, joined by a tapered section **26** to a head portion **28** having a substantially flat lower face **30** which has an outer annular drive surface **32** arranged to engage upon and drive an actuation pin **34** of a dose counter **36** as will be described. Extending centrally and axially from the lower face **30** is a valve stem **38** which is arranged to sealingly engage in a valve stem block **40** of the main body **10** of the inhaler **12**. The valve stem block **40** has a passageway **42** leading to a nozzle **44** for directing the contents of the canister **20**, namely active drug and propellant, towards an air outlet **46** of the inhaler main body **12**. It will be appreciated that due to gaps **48** between the canister **20** and an inner wall **50** of the main body **10** of the inhaler **12** an open top **52** of the main body **10** forms an air inlet into the inhaler **12** communicating via air passageway **54** with the air outlet **46**, such that canister contents exiting nozzle **44** mix with air being sucked by the user through the air passageway **54** in order to pass together through the air outlet and into the mouth of the user (not shown).

The dose counter **36** will now be described. The dose counter **36** includes an actuation pin **34** biased upwardly from underneath by a return spring **56** once installed in the main body **10**. As best shown in FIGS. **4**A, **6**H and **8**A, the pin **34** has side surfaces **58**, **60** arranged to slide between corresponding guide surfaces **62**, **64** located in a dose counter chamber **66** of the main body **10**, as well as an end stop surface **68** arranged to engage a corresponding end stop **70** formed in the dose counter chamber **66** to limit upward movement of the pin **34**. The pin **34** has a top part **72** which is circularly cylindrical and extends through an aperture **74** formed through a separator wall **76** which separates the canister chamber **18** from the dose counter chamber **66**. The top part **72** of the pin **34** has a flat top surface **78** which is arranged to engage the outer annular drive surface **32** of the canister **20**.

The actuation pin **34** is integrally formed with a drive or actuator pawl **80**. The actuator pawl **80** has a generally inverted U-shape configuration, having two mutually spaced and parallel arms **82**, **84** extending from a base portion of the actuation pin **34**, each holding at respective distal ends **88** thereof opposite ends of a pawl tooth member **90** which extends in a direction substantially perpendicular to the arms **82**, **84**, so as to provide what may be considered a "saddle" drive for pulling on each of the 11 drive teeth **92** of a ratchet wheel **94** of an incremental drive system **96** or ratchet mechanism **96** of the dose counter **36**. As shown for example in FIG. **10**B, the pawl tooth member **90** has a sharp lower longitudinal side edge **98** arranged to engage the drive teeth **92**, the edge-to-surface contact provided by this engagement

providing very accurate positioning of the actuator pawl **80** and resultant rotational positioning of the ratchet wheel **94**.

The dose counter **36** also has a chassis preassembly **100** which, as shown in FIGS. **4**A and **6**A, includes a chassis **102** having a first shaft **104** receiving the ratchet wheel **94** which is secured to a tape reel shaft **106**, and a second shaft (or split pin) **108** which is parallel to and spaced from the first shaft **104** and which slidably and rotationally receives a tape stock bobbin **110**.

As shown in FIG. **6**B, when the inhaler has not been used at all, the majority of a tape **112** is wound on the tape stock bobbin **110** and the tape **112** has a series of regularly spaced numbers **114** displayed therealong to indicate a number of remaining doses in the canister **20**. As the inhaler is repeatedly used, the ratchet wheel **94** is rotated by the actuator pawl **80** due to operation of the actuation pin **34** by the canister **20** and the tape **112** is incrementally and gradually wound on to the tape reel shaft **106** from the second shaft **108**. The tape **112** passes around a tape guide **116** of the chassis **102** enabling the numbers **114** to be displayed via a window **118** in a dose counter chamber cover **120** having a dose marker **132** formed or otherwise located thereon.

As shown in FIGS. **6**A and **6**D, the second shaft **108** is forked with two forks **124**, **126**. The forks **124**, **126** are biased away from one another. The forks have located thereon at diametrically opposed positions on the second shaft **108** friction or control elements **128**, **130**, one on each fork. Each control element extends longitudinally along its respective fork **124**, **126** and has a longitudinally extending friction surface **132**, **134** which extends substantially parallel to a longitudinal axis of the second shaft and is adapted to engage inside a substantially cylindrical bore **136** inside the tape stock bobbin **110**. This control arrangement provided between the bore **136** and the control elements **128**, **130** provides good rotational control for the tape stock bobbin **110** such that it does not unwind undesirably such as when the inhaler is dropped. The tape force required to unwind the tape stock bobbin **110** and overcome this friction force is approximately 0.1 N.

As can be seen in FIG. **6**D, as well as FIGS. **6**G and **10**A to **10**F, the chassis **102** is provided with an anti-back drive tooth **138** or count pawl **138** which is resiliently and substantially fixedly mounted thereto. As will be described below and as can be seen in FIGS. **10**A to **10**F, when the actuation pin **34** is depressed fully so as to fire the metered valve (not shown) inside the canister **20**, the actuator pawl **80** pulls down on one of the teeth **92** of the ratchet wheel **94** and rotates the wheel **94** anticlockwise as shown in FIG. **6**D so as to jump one tooth **92** past the count pawl **138**, thereby winding the tape **112** a distance incrementally relative to the dose marker **122** on the dose counter chamber **120** so as to indicate that one dose has been used.

With reference to FIG. **10**B, the teeth of the ratchet wheel **94** have tips **143** which are radiused with a 0.1 mm radius between the flat surfaces **140**, **142**. The ratchet wheel **94** has a central axis **145** which is 0.11 mm above datum plane **220** (FIG. **9**). A top/nose surface **147** of the anti-back drive tooth **138** is located 0.36 mm above the datum plane **220**. The distance vertically (i.e. transverse to datum plane **220**—FIG. **9**) between the top nose surface **147** of the anti-back drive tooth is 0.25 mm from the central axis **145** of the wheel **94**. Bump surface **144** has a lateral extent of 0.20 mm, with a vertical length of a flat **145'** thereof being 1 mm, the width of the bump surface being 1.22 mm (in the direction of the axis **145**), the top **149** of the bump surface **144** being 3.02 mm vertically below the axis **145**, and the flat **145'** being spaced a distance sideways (i.e. parallel to the datum plane **220**) 2.48 mm from the axis **145**. The top surface **78** of the pin **34** (FIG. **6**H) is 11.20 mm above the datum plane **220** (FIG. **9**) when the actuator pawl **80** and pin **34** are in the start configuration. The length of the valve stem **22** is 11.39 mm and the drive surface **32** of the canister **20** is 11.39 mm above the datum plane **220** when the canister is at rest waiting to be actuated, such that there is a clearance of 0.19 mm between the canister **20** and the pin **34** in this configuration.

FIGS. **10**A and **10**B show the actuator pawl **80** and ratchet wheel **94** and count pawl **138** in a start position in which the flat top **78** of the pin **34** has not yet been engaged by the outer annular drive surface **32** of the canister **20** or at least has not been pushed down during a canister depression.

In this "start" position, the count pawl **138** engages on a non-return back surface **140** of one of the teeth **92** of the ratchet wheel **94**. The lower side edge **98** of the actuator pawl is a distance "D" (FIG. **9**) 1.33 mm above datum plane **220** which passes through bottom surface or shoulder **41** of valve stem block **40**, the datum plane **220** being perpendicular to a main axis "X" of the main body **10** of the inhaler **12** which is coaxial with the centre of the valve stem block bore **43** and parallel to a direction of sliding of the canister **20** in the main body **10** of the inhaler **12** when the canister is fired.

As shown in FIG. **10**B, an advantageous feature of the construction is that the pawl tooth/actuator **90** acts as a supplementary anti-back drive member when the inhaler **12** is not being used for inhalation. In particular, if the inhaler **12** is accidentally dropped, resulting in a jolt to the dose counter **36** then, if the wheel **94** would try to rotate clockwise (backwards) as shown in FIG. **10**B, the back surface **140** of a tooth will engage and be blocked by the tooth member **90** of the pawl **80**. Therefore, even if the anti-back drive tooth **138** is temporarily bent or overcome by such a jolt, undesirable backwards rotation of the wheel **94** is prevented and, upon the next canister firing sequence, the pawl **90** will force the wheel **94** to catch up to its correct position so that the dose counter **36** continues to provide correct dosage indication.

FIG. **10**C shows a configuration in which the actuator pawl **80** has been depressed with the pin **34** by the canister **20** to a position in which the side edge **98** of the pawl tooth member **90** is just engaged with one of the teeth **92** and will therefore upon any further depression of the pin **34** begin to rotate the wheel **94**. This is referred to as a "Reset" position or configuration. In this configuration, the lower side edge **98** of the actuator **80** is 0.64 mm above the datum plane **220**.

FIG. **10**D shows a configuration in which the actuator pawl **80** has been moved to a position lower than that shown in FIG. **10**C and in which the metered dose valve (not shown) inside the canister has at this very position fired in order to eject active drug and propellant through the nozzle **44**. It will be noted that in this configuration the count pawl **138** is very slightly spaced from the back surface **140** of the same tooth **92** that it was engaging in the configuration of FIG. **10**D. The configuration shown in FIG. **10**D is known as a "Fire" configuration. In this configuration the lower side edge **98** of the actuator **80** is 0.47 mm below the datum plane **220**.

FIG. **10**E shows a further step in the sequence, called a "Count" position in which the actuator pawl **80** has rotated the ratchet wheel **94** by the distance circumferentially angularly between two of the teeth **92**, such that the count pawl **138** has just finished riding along a forward surface **142** of one of the teeth **92** and has resiliently jumped over the tooth into engagement with the back surface **140** of the next tooth. Accordingly, in this "Count" configuration, a sufficiently

long stroke movement of the pin **34** has occurred that the tape **112** of the dose counter **36** will just have counted down one dose. In this configuration, the lower side edge **98** of the actuator is 0.95 mm below the datum plane **220**. Accordingly, in this position, the actuator **80** generally, including edge **98**, is 0.48 mm lower than in the fire configuration. It has been found that, although the count configuration happens further on than the fire configuration, counting is highly reliable, with less than one in 50 failed counts per million. This is at least partially due to momentum effects and to the canister releasing some back pressure on the user in some embodiments as its internal metering valve fires.

In the configuration of FIG. **10**F, the pawl **80** has been further depressed with the pin **34** by the canister **20** to a position in which it is just disengaging from one of the teeth **92** and the actuator pawl **80** is assisted in this disengagement by engagement of one of the arms **84** with a bump surface **144** on the chassis **102** (see FIG. **6**G) and it will be seen at this point of disengagement, which is called an "End" configuration, the count pawl **138** is positioned exactly halfway or substantially halfway between two of the drive teeth **92**. This advantageously means therefore that there is a minimum chance of any double counting or non-counting, which would be undesirable. In the end configuration, the side edge **98** of the actuator is 1.65 mm below the datum plane **220**. It will be appreciated that any further depression of the actuator pawl **80** and pin **34** past the "End" configuration shown in FIG. **10**F will have no effect on the position of the tape **112** displayed by the dose counter **36** since the actuator pawl **80** is disengaged from the ratchet wheel **94** when it is below the position shown in FIG. **10**F.

As shown in FIGS. **7**C and **7**D, the inner wall **50** of the main body **10** is provided with a two-step support rail **144** which extends longitudinally along inside the main body and is located directly adjacent the aperture **74**. As shown in FIG. **7**B a diametrically opposed two-step support rail **146** is also provided and this diametrically opposed in the sense that a vertical plane (not shown) can pass substantially directly through the first rail **144**, the aperture **74**, a central aperture **148** of the valve stem block **40** (in which canister stem **25** is located) and the second two-step support rail **146**. As shown in FIG. **7**A and schematically in FIG. **7**B, the rails **144**, **146** provide a maximum clearance between the canister **20** and the rails **144**, **146** in a radial direction of almost exactly 0.3 mm, about 0.25 to 0.35 mm being a typical range. This clearance in this plane means that the canister **20** can only rock backwards and forwards in this plane towards away from the actuation pin **34**. A relatively small distance and this therefore prevents the canister wobbling and changing the height of the actuation pin **34** a as to undesirably alter the accuracy of the dose counter **36**. This is therefore highly advantageous.

The inner wall **50** of the main body **10** is provided with two further two-step rails **150** as well as two pairs **152**, **154** of rails extending different constant radial amounts inwardly from the inner wall **50**, so as to generally achieve a maximum clearance of almost exactly 0.3 mm around the canister **20** for all of the rails **144**, **146**, **150**, **152**, **154** spaced around the periphery of the inner wall **50**, in order to prevent undue rocking while still allowing canister motion freely inside the inhaler **12**. It will be clear from FIG. **7**C for example that the two-step rails have a first portion near an outlet end **156** of the canister chamber **18**, the first portion having a substantially constant radial or inwardly-extending width, a first step **160** leading to a second portion **162** of the rail, the second portion **102** having a lesser radial or inwardly extending extent than the first portion **156**, and finally a second step **164** at which the rail merges into the main inner wall **50** main surface.

A method of assembling the inhaler **12** will now be described.

With reference to FIG. **8**A, the main body **10** of the inhaler **12** is formed by two or more plastics mouldings which have been joined together to the configuration shown.

As shown in FIG. **8**B, the actuator pawl **80** and pin **34** are translated forward into position into a pin receiving area **166** in the dose counter chamber **66** and the pin **34** and actuator **80** may then be raised until the pin **34** emerges through the aperture **74**.

Next, the return spring **56** may be inserted below the pin **34** and a generally cylindrical annular lower end **168** of the spring **56** may be moved by a tweezer or tweezer-like assembly tool (not shown) into engagement with a shelf **170** of a spring retainer **172** in the dose counter chamber **66**. The spring retainer **172** is U-shaped and the shelf **170** is U-shaped and has a recess **174** formed below it. As shown in FIGS. **4**B, **4**C and **12** shelf **170** includes three chamfer surfaces **176**, **178**, **180** arranged to assist in moving the lower end of the spring **168** into position onto the shelf using the assembly tool (not shown). Once the lower end of the spring **168** is in place, the assembly tool (not shown) can easily be removed at least partly via the recess **174** below the lower end **168** of the spring **56**.

The tape **112** is attached at one end (not shown) to the tape stock bobbin **110** and is wound onto the bobbin by a motor **200** (FIG. **13**) having a hexagonal output shaft **202** which engages in a hexagonal socket **204** (FIG. **6**B) of the bobbin. During winding, the tape is monitored by a sensor **206**, which may be in the form of a camera or laser scanner, which feeds data to a computer controller **205** for the motor **200**. The controller **205** recognises three positioning markers **210** in the form of lines across the tape **112** and stops the motor **202** when the tape **112** is nearly fully wound onto the bobbin **110**, such that the distal end **212** of the tape **112** can be secured, e.g. by adhesive, to the tape reel shaft **106**. The controller **205** also recognises a pixelated tape size marker **214** observed by the sensor **206** and logs in a stocking system data store **217** details of the tape **112** such as the number of numbers **114** on the tape, such as one hundred and twenty or two hundred numbers **114**. Next, the tape reel shaft is wound until an appropriate position of the lines **210** at which a priming dot **216** will, once the bobbin **110** and reel shaft **106** are slid onto the second shaft **108** and second shaft **104**, be in a position to be located in the window **118** when the inhaler **12** is fully assembled. In the embodiments, the bobbin **110** and reel shaft **106** may be slid onto the shafts **108**, **104** before the tape **112** is secured to the reel shaft **106** and the reel shaft may then be wound to position the priming dot **216**.

Next, the assembled dose counter components of the chassis preassembly **100** shown in FIG. **6**B may as shown in FIG. **8**C be inserted into the dose counter chamber **66**, with pins **182**, **184**, **186** formed on the main body **10** in the dose counter chamber **66** passing through apertures or slots **188**, **190**, **192** formed on the chassis **102**, such that the pins **182**, **184**, **186** extend through (or at least into) the apertures or slots **188**, **190**, **192**. With the chassis **102** being relatively firmly pushed towards the main body **10**, the pins **182**, **184**, **186** are then heat staked and the chassis **102** is therefore after this held very firmly in position in the main body and is unable to move, thereby assisting in providing great accuracy for the dose counter **36**. Next, as shown in FIG. **8**D, the dose counter chamber cover **120** may be fitted over the dose

counter chamber **66** and may be secured in place such as by welding, with the priming dot **216** being displayed through the window.

The user can, when readying the inhaler **12** for first use, prime the inhaler by depressing the canister **20** three times which will bring the first number **114** on the tape into display through the window **118** in place of the priming dot **216**, the number **114** shown in FIG. **8**D being "200", thereby indicating that 200 doses are remaining to be dispensed from the canister **20** and inhaler **12**.

As shown in FIG. **8**D, and in FIG. **5**, an open drain hole **194** is provided at the bottom of the dose counter chamber **66** by a substantially semi-circular cut-out or recess formation **196** in a lower surface **198** of the main body **10** of the inhaler. Accordingly, if the user (not shown) should decide to wash the main body **10** of the inhaler, for example after encountering an unhygienic situation or simply as a matter of choice, the drain hole **194** allows initial draining of water from inside the dose counter chamber **66** and also thereafter evaporation of water or any aqueous matter in the dose counter chamber **66** so that the window **118** does not mist up undesirably.

FIG. **14** shows a computer system **230** for designing the dose counter **36** and in particular for calculating distributions representative of average positions and standard deviations in a production series of inhalers of the start, reset, fire, count and end positions of the actuator lower side edge **98** relative to the datum plane **220** (FIG. **9**) and therefore of the actuator pawl **80** generally relative to the ratchet wheel **94**, chassis **102** and, when the inhaler **12** is fully assembled, the main body **10** of the inhaler **12**. The computer system **230** includes a data store **232**, a CPU **234**, an input device **236** (such as a keyboard or communication port) and an output device **238** (such as a communications port, display screen and/or printer). A user may enter data via the input device **236** which may be used by the CPU **234** in a mathematical calculation to predict count failure rates when the various dose counters are to be built in a series with dose counter positions set with given averages and standard deviations and taking into account any momentum/inertia effects and metering valve user-back-pressure reduction effect which will occur upon canister firing of a given type of canister. The computer system **230** is thus mathematically used to design the distributions. For the inhaler **12** described herein with the dose counter **36** and canister **20**, the distributions are designed as shown in FIG. **11**. The x axis shows distance of the lower side surface **98** of the actuator **80** above the datum plane **220** and the y axis is representative of the distribution. Thus, curve **240** shows that the start configuration has an average 1.33 mm above the datum plane **200** (standard deviation is 0.1 mm), curve **242** shows that the reset configuration has an average of 0.64 mm above the datum plane **220** (standard deviation is 0.082 mm), curve **244** shows the fire configuration has an average 0.47 mm below the datum plane **220** (standard deviation is 0.141 mm), curve **246** shows the count configuration has an average 0.95 mm below the datum plane **220** (standard deviation is 0.080 mm), and curve **248** shows the end configuration has an average of 1.65 mm below the datum plane **220** (standard deviation is 0.144 mm).

FIGS. **15** to **20** show a version of the inhaler modified in accordance with the present invention. In these drawings, the same reference numerals have been used to those in the earlier drawings to denote the equivalent components. The inhaler **12** is the same as that in FIGS. **1** to **14** apart from the following modifications.

First, it can be seen that there is a modification in that the drive teeth **92** of the ratchet wheel **94** have a different profile to that in FIGS. **1** to **14**. There are also only nine ratchet teeth **94** in this embodiment instead of eleven.

Additionally, as shown in FIGS. **18**C and **19**C, the control elements **128**, **130** on the forks **124**, **126** of the second shaft **108** have a tapered profile which is different to the profile of the control elements **128**, **130** shown in FIG. **6**F. Either profile can be used in the embodiment of FIGS. **15** to **20** however.

Furthermore, as shown in FIG. **15**, the tape stock bobbin **110** has an inwardly facing generally cylindrical engagement surface **300** with a wavelike form extending partially therealong. The engagement surface **300** has a cross-section **301** perpendicular to the longitudinal length of the stock bobbin **110** which is constant therealong. This cross-section **301** can be seen in FIG. **16** and consists of a series of ten regularly spaced concavities **302** and ten convex wall portions **304**. The convex wall portions **304** are equi-spaced between the concavities **302**. Each concavity **302** has a radius of 0.2 mm. Each convex wall portion **304** also has a radius of 0.2 mm. Finally, the cross section **301** also includes flat wall portions **306** between all of the radiused wall portions of the concavities **302** and convex wall portions **304**. The geometry of the cross-section **301** is therefore defined by the radii of the concavities **302** and convex wall portions **304**, the flat wall portions **306** and the fact that there are ten concavities **302** and convex wall portions **304**.

The minor diameter of the engagement surface **300**, i.e. between the tips of opposite convex wall portions **304**, is 2.46 mm. The major diameter of the engagement surface **300**, i.e. between the outermost portions of the concavities **302**, is 2.70 mm. The undeformed tip to tip maximum diameter of the forks **124**, **126** of the split pin (the second shaft) **108**, i.e. in the region of the maximum radio extent of the control elements **128**, **130**, is 3.1 millimeters and it will therefore be appreciated that the forks **124**, **126** are resiliently compressed once the stock bobbin **110** has been assembled onto the split pin **108** in all rotational configurations of the stock bobbin **110** relative to the split pin **108**. The minimum gap between the forks **124**, **126** in the plane of the cross sections of FIGS. **18**C and **19**C is 1 mm when the split pin **108** is in the undeformed, pre-inserted state. When the split pin **108** is at maximum compression, as shown in FIGS. **18**A to **18**C when the control elements **128**, **130** are shown to be engaged on top of the convex wall portions **304**, the gap **308** between the tips **310**, **312** of the forks **124**, **126** is 0.36 mm. On the other hand, when the split pin **108** is at minimum compression (once inserted into the stock bobbin) as shown in FIGS. **19**A to **19**C, when the control elements **128**, **130** rest in the concavities **302**, the gap between the tips **310**, **312** of the forks **124**, **126** is 0.6 mm. The control elements **128**, **130** are outwardly radiused with a radius also of 0.2 mm such that they can just rest on the concavities **302** with full surface contact (at least at an axial location on the split pin where the tapered control elements are at their maximum radial extent), without rattling in, locking onto or failing to fit in the concavities **302**. The radii of the control elements **128**, **130** is therefore preferably substantially the same as the radii of the concavities **302**

It will be appreciated that whereas FIGS. **18**B and **19**B are end views along the coaxial axis of the stock bobbin **110** and split pin **108**, FIGS. **18**A and **19**A are cross-sections. FIG. **19**A is a section on the plane A-A' in FIG. **19**C and FIG. **18**A is a section at the same plane, but of course with the stock bobbin **110** rotated relative to the split pin **108**.

As the inhaler **12** is used and the ratchet wheel **94** rotates in order to count used doses, the stock bobbin rotates incrementally through rotational positions in which rotation is resisted, i.e. due to increasing compression of the split pin **108** at such rotational positions, and rotational positions in which rotation is promoted, i.e. due to decreasing compression of the split pin **108** at such rotational positions and this may involve a click forward of the stock bobbin **110** to the next position equivalent to that in FIGS. **19**A to **19**C in which the control elements **128**, **130** of the split pin art located in the concavities **302**. This functionality firstly allows the stock bobbin to unwind during use as required, but also prevents the tape **112** from loosening during transit if the inhaler **12** is dropped, such as onto a hard surface. This is highly advantageous, since the tape **11** is prevented from moving to a position in which it will give an incorrect reading regarding the number of doses in the canister.

During compression and expansion of the forks in the radial direction between the two configurations shown in FIGS. **18**C and **19**C, the forks **124**, **126** rotate about a point **316** on the split pin where the forks **124**, **126** come together. This rotational action means that there is a camming action between the forks **124**, **126** and the engagement surface **300** without significant friction but, nevertheless, the resilient forces provided by the regulator formed by the engagement surface **300** and forks **124**, **126** are able to regulate unwinding of the tape such that it does not easily occur during transit or if the inhaler **12** is dropped. It has been found during testing that a force of 0.3 to 0.4 N needs to be applied to the tape **112** to overcome the regulator at the stock bobbin **110**. 0.32 N is achieved with the control elements **128** having the profile shown in FIG. **19**C and 0.38 N is achieved with the profile of the control elements **128** altered to be as shown as described with reference to FIG. **6**F. These forces are substantially higher than the 0.1 N force mentioned above and undesirable movement of the tape is substantially avoided even if the inhaler is dropped onto a hard surface. The modified arrangement of FIGS. **15** to **20** does not provide this force "constantly" such that there is overall not an undesirably high friction of the tape **112** as it passes over the other components of the dose counter because, due to the incremental nature of the resilient forces at the regulator, the tape **112** can incrementally relax as it slides over the stationary chassis components.

Instead of having ten concavities **302** and convex wall portions **304**, other numbers may be used, such as 8 or 12. However, it is preferred to have an even number, especially since two control elements **128**, **130** are provided, so that all of the control elements **128**, **130** will expand and contract simultaneously. However, other arrangements are envisaged with 3 or more forks and the number of concavities/convex wall portions may be maintained as an integer divisible by the number of forks to maintain a system with simultaneous expansion/contraction. For example, the use of 9, 12 or 15 concavities/convex wall portions with 3 forks is envisaged.

Instead of having the engagement surface **300** on the inside of the stock bobbin **110**, it could be placed on the outside of the stock bobbin **110** so as to be engaged by flexible external legs/pawls or similar.

It will be noted that the regulator provided by the engagement surface **300** and forks **124**, **126** does not only allow rotation of the stock bobbin in one direction as is the case with the ratchet wheel **94**. Rotation in both directions is possible, i.e. forwards and backwards. This means that during assembly, the stock bobbin **110** can be wound backwards during or after fitting the bobbin **100**, shaft **106** and tape **112** onto the carriage **102**, if desired.

The stock bobbin **110** and the carriage **102** including the split pin **108** are both moulded of polypropylene material.

It will be seen from FIG. **16** that the cross-sectional shape **301** is not symmetrical within the hexagonal socket **204**. This has enabled the hexagonal socket **204** to be maintained at a useful size while still allowing the desired size and geometry of the cross section **301** to fit without interfering with the hexagonal shape of the hexagonal socket **204** and also permits moulding to work during manufacture.

As shown in FIG. **17**, the stock bobbin **110** has a series of four circumferential ribs **330** inside it and a spaced thereabout. These hold the stock bobbin **110** on the correct side of the mould tool during moulding.

FIGS. **21** and **22** show a preferred embodiment in accordance with the invention of an inhaler **510** for dispensing a dry-powdered medicament in metered doses for patient inhalation. The inhaler **510** is as disclosed in FIGS. **1** to **16** or EP-A-1330280, the contents of which are hereby fully incorporated herein by reference, but with the stock bobbin **110** and second shaft **108** of the dose counter **516** modified so as to be as in FIGS. **15** to **20** hereof. Thus, the dry powder inhaler **510** generally includes a housing **518**, and an assembly **512** received in the housing (see FIG. **21**). The housing **518** includes a case **520** having an open end **522** and a mouthpiece **524** (FIG. **25**) for patient inhalation, a cap **526** secured to and closing the open end **522** of the case **520**, and a cover **528** pivotally mounted to the case **520** for covering the mouthpiece **524**. As shown in FIG. **22**, the inhaler **510** also includes an actuation spring **569**, first yoke **566** with opening **572**, bellows **540** with crown **574**, a reservoir **514**, second yoke **568** with hopper **542** and dose counter **516** mounted thereto, and case **520** has transparent window **5130** thereon for viewing dose counter tape indicia **5128**. The dose metering system also includes two cams **570** mounted on the mouthpiece cover **528** and movable with the cover **528** between open and closed positions. The cams **570** each include an opening **580** for allowing outwardly extending hinges **582** of the case **520** to pass therethrough and be received in first recesses **584** of the cover **528**. The cams **570** also include bosses **586** extending outwardly and received in second recesses **588** of the cover **528**, such that the cover **528** pivots about the hinges **582** and the cams **570** move with the cover **528** about the hinges **582**. As described in EP-A-1330280, cams **570** act upon cam followers **578** to move second yoke **568** up and down and thereby operate dose counter by engagement of pawl **5138** on the second yoke **568** with teeth **5136**. Remaining components of the inhaler are provided as, and operate as described, in EP-A-1330280.

The dose counting system **516** therefore includes a ribbon or tape **5128** (FIGS. **23** & **24**), having successive numbers or other suitable indicia printed thereon, in alignment with a transparent window **5130** provided in the housing **18** (see FIG. **22**). The dose counting system **516** includes the rotatable stock bobbin **110** (as described above), an indexing spool **5134** rotatable in a single direction, and the ribbon **5128** rolled and received on the bobbin **110** and having a first end **5127** secured to the spool **5134**, wherein the ribbon **5128** unrolls from the bobbin **110** so that the indicia are successively displayed as the spool **5134** is rotated or advanced. In FIGS. **23** and **24** the wavelike engagement surface **300** of the bobbin **110** is not shown for the purposes of clarity.

The spool **134** is arranged to rotate upon movement of the yokes **566**, **568** to effect delivery of a dose of medicament from reservoir **514**, such that the number on the ribbon **5128** is advanced to indicate that another dose has been dispensed by the inhaler **510**. The ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase or

decrease upon rotation of the spool **5134**. For example, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, decrease upon rotation of the spool **5134** to indicate the number of doses remaining in the inhaler **510**. Alternatively, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase upon rotation of the spool **5134** to indicate the number of doses dispensed by the inhaler **10**.

The indexing spool **5134** includes radially extending teeth **5136**, which are engaged by pawl **5138** extending from a cam follower **578** of the second yoke **568** upon movement of the yoke to rotate, or advance, the indexing spool **5134**. More particularly, the pawl **5138** is shaped and arranged such that it engages the teeth **5136** and advances the indexing spool **5134** only upon the mouthpiece cover **528** being closed and the yokes **566**, **568** moved back towards the cap **526** of the housing **518**.

The dose counting system **516** also includes a chassis **5140** that secures the dose counting system to the hopper **542** and includes shafts **108**, **5144** for receiving the bobbin **110** and the indexing spool **5134**. As described above with reference to FIGS. **1** to **20**, the bobbin shaft **108** is forked and includes radially nubs **5146** for creating a resilient resistance to rotation of the bobbin **110** on the shaft **108** by engaging with the wavelike engagement surface **300** inside the bobbin **110**. A clutch spring **5148** is received on the end of the indexing spool **5134** and locked to the chassis **5140** to allow rotation of the spool **5134** in only a single direction.

Various modifications may be made to the embodiment shown without departing from the scope of the invention as defined by the accompanying claims as interpreted under patent law.

What is claimed:

1. An inhaler for metered dose inhalation, the inhaler comprising:

a main body having a canister housing,

a medicament canister, which is moveable relative to the canister housing and retained in a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister, and

a dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,

wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall, and

wherein the canister housing has a longitudinal axis X which passes through the center of the central outlet port,

the inner wall canister support formation, the actuation member, and the central outlet port lying in a common plane coincident with the longitudinal axis X.

2. The inhaler as claimed in claim **1** wherein the medicament canister is movable relative to the dose counter.

3. The inhaler as claimed in claim **1** further comprising an aperture formed in the inner wall through which the portion of the actuation member extends.

4. The inhaler as claimed in claim **1**, wherein the first inner wall canister support formation comprises a support rail which extends longitudinally along an inside surface of the main body.

5. The inhaler as claimed in claim **4**, wherein the support rail includes a step formed thereon.

6. The inhaler as claimed in claim **4** further comprising a plurality of support rails each of which extends longitudinally along an inside surface of the main body.

7. The inhaler as claimed in claim **6**, wherein two of the plurality of support rails are positioned at opposite ends of the inside surface of the main body to face each other.

8. The inhaler as claimed in claim **4**, wherein the support rail includes two steps formed thereon, the steps being spaced apart longitudinally along an inside surface of the main body.

9. The inhaler as claimed in claim **4**, wherein the support rail merges with the inner wall at a location adjacent the aperture.

10. The inhaler as claimed in claim **9**, wherein a width dimension of the support rail is not constant, and the width dimension is greatest at the location where the support rail merges with the inner wall.

* * * * *

EXHIBIT 2

9475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 9, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: *9,808,587*
ISSUE DATE: *November 7, 2017*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

John Burson
Certifying Officer

US009808587B2

(12) **United States Patent**
Walsh et al.

(10) **Patent No.: US 9,808,587 B2**
(45) **Date of Patent: *Nov. 7, 2017**

(54) **DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR**

(71) Applicants: **IVAX PHARMACEUTICALS IRELAND**, Waterford (IE); **NORTON (WATERFORD) LIMITED**, Waterford (IE); **TEVA PHARMACEUTICALS IRELAND**, Waterford (IE)

(72) Inventors: **Declan Walsh**, Co. Kilkenny (IE); **Derek Fenlon**, Co. Wexford (IE); **Simon Kaar**, Co. Cork (IE); **Jan Geert Hazenberg**, Co. Kilkenny (IE); **Daniel Buck**, Co. Waterford (IE); **Paul Clancy**, Waterford (IE); **Robert Charles Uschold**, Leominster, MA (US); **Jeffrey A. Karg**, Hopkinton, MA (US)

(73) Assignees: **IVAX PHARMACEUTICALS IRELAND** (IE); **TEVA PHARMECUTICALS IRELAND** (IE); **NORTON (WATERFORD) LIMITED** (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/269,249**

(22) Filed: **Sep. 19, 2016**

(65) **Prior Publication Data**

US 2017/0000962 A1 Jan. 5, 2017

Related U.S. Application Data

(60) Continuation of application No. 14/103,324, filed on Dec. 11, 2013, now Pat. No. 9,463,289, which is a (Continued)

(51) **Int. Cl.**
G06M 1/06 (2006.01)
A61M 11/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC *A61M 15/0078* (2014.02); *A61M 11/00* (2013.01); *A61M 15/009* (2013.01);
(Continued)

(58) **Field of Classification Search**
USPC 235/8, 103; 128/200.23
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,174,890 A 11/1979 Johnson
4,669,838 A 6/1987 Hibbard
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2501726 9/2006
EP 1330280 7/2003
(Continued)

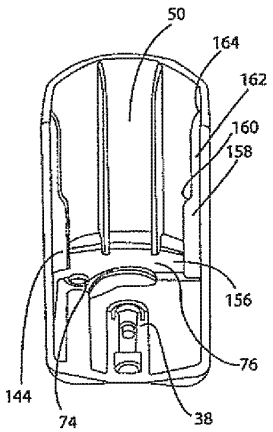
OTHER PUBLICATIONS

Final Office Action dated Oct. 20, 2016 for U.S. Appl. No. 14/699,567.
(Continued)

Primary Examiner — Daniel Hess
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

An inhaler includes a main body having a canister housing, a medicament canister retained in a central outlet port of the canister housing, and a dose counter having an actuation member for operation by movement of the medicament canister. The canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall. The canister housing
(Continued)



has a longitudinal axis X which passes through the center of the central outlet port. The first inner wall canister support formation, the actuation member, and the central outlet port lie in a common plane coincident with the longitudinal axis X such that the first inner wall canister support formation protects against unwanted actuation of the dose counter by reducing rocking of the medicament canister relative to the main body of the inhaler.

22 Claims, 17 Drawing Sheets

Related U.S. Application Data

division of application No. 13/110,532, filed on May 18, 2011, now Pat. No. 8,978,966.

(60) Provisional application No. 61/417,659, filed on Nov. 29, 2010, provisional application No. 61/345,763, filed on May 18, 2010.

(51) **Int. Cl.**
A61M 15/00 (2006.01)
G06M 1/24 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 15/0025*** (2014.02); ***A61M 15/0026*** (2014.02); ***A61M 15/0065*** (2013.01); ***A61M 15/0071*** (2014.02); ***G06M 1/246*** (2013.01); *A61M 2202/064* (2013.01); *A61M 2205/6063* (2013.01); *A61M 2207/00* (2013.01); *A61M 2207/10* (2013.01); *Y10T 29/49* (2015.01); *Y10T 29/49764* (2015.01); *Y10T 29/49826* (2015.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,687,359	A	8/1987	Barrus	
5,482,030	A	1/1996	Klein	
5,861,911	A	1/1999	Oosaka	
6,446,627	B1	9/2002	Bowman	
6,718,972	B2	4/2004	OLeary	
8,418,690	B2	4/2013	Power	
8,474,448	B2	7/2013	Oi	
8,978,966	B2	3/2015	Walsh et al.	
9,174,013	B2	11/2015	Walsh et al.	
9,463,289	B2 *	10/2016	Walsh	A61M 15/0065
2002/0047021	A1	4/2002	Blacker	
2002/0078949	A1	6/2002	OLeary	
2002/0078950	A1	6/2002	OLeary	
2002/0084891	A1	7/2002	Mankins et al.	
2003/0209239	A1	11/2003	Rand	
2004/0089298	A1	5/2004	Haikarainen et al.	
2004/0095746	A1	5/2004	Murphy	
2005/0028815	A1	2/2005	Deaton	
2005/0087191	A1 *	4/2005	Morton	A61M 15/0065 128/205.23
2006/0096594	A1	5/2006	Bonney	
2006/0107949	A1 *	5/2006	Davies	A61M 15/0065 128/200.23
2006/0107979	A1	5/2006	Kim	
2007/0062518	A1	3/2007	Geser	
2008/0242465	A1	10/2008	Strobel	
2009/0178678	A1	7/2009	OLeary	
2010/0089395	A1	4/2010	Power	
2010/0218759	A1	9/2010	Anderson	
2011/0041845	A1	2/2011	Solomon	
2012/0006322	A1	1/2012	Anderson	

FOREIGN PATENT DOCUMENTS

EP	1486227		12/2004
GB	2320489		6/1998
IL	201256		11/2014
JP	02502129		7/1990
JP	450059		8/1992
JP	07100205		4/1995
JP	10504220		4/1998
JP	2002528144		9/2002
JP	2004501685		1/2004
JP	2008-94103	A	4/2008
JP	2008094103		4/2008
JP	2008261423		10/2008
JP	2009233308		10/2009
JP	2009257392		11/2009
JP	2010096308		4/2010
WO	8909078		10/1989
WO	9628205		9/1996
WO	9828033		7/1998
WO	9936115		7/1999
WO	02/00281	A2	1/2002
WO	03101514		12/2003
WO	2005102430		11/2005
WO	2006062449		6/2006
WO	2006062449	A1	6/2006
WO	2007012861		2/2007
WO	2007062518		6/2007
WO	2008023019		2/2008
WO	2008119552		2/2008
WO	2011012325		2/2011
WO	2011012327		2/2011

OTHER PUBLICATIONS

Advisory Action dated Mar. 13, 2017 for U.S. Appl. No. 14/699,567.
Non-Final Office Action dated Jan. 12, 2017 for U.S. Appl. No. 14/713,620, 8 pages.
Final Rejection dated Sep. 27, 2016 for U.S. Appl. No. 14/699,578.
Final Office Action dated Aug. 31, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Advisory action dated Feb. 9, 2017 for U.S. Appl. No. 14/699,584.
Non-final rejection dated Jul. 12, 2016 for U.S. Appl. No. 14/713,643.
File History for U.S. Appl. No. 15/271,738.
File History for U.S. Appl. No. 15/269,102.
File History for U.S. Appl. No. 15/262,818.
File History for U.S. Appl. No. 15/289,553.
File History for U.S. Appl. No. 15/269,249.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/699,584.
Non-Final Office Action dated Jun. 24, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/713,631.
Advisory Action dated Mar. 16, 2017 or U.S. Appl. No. 14/713,633.
Entire patent prosecution history of U.S. Appl. No. 13/110,532, filed May 18, 2011, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,324, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,343, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,353, filed Dec. 11, 2013, entitled,"Dose Counters for Inhalers, Inhalers and Methods of Ass Embly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,363, filed Dec. 1, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,392, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".

(56) **References Cited**

OTHER PUBLICATIONS

Entire patent prosecution history of U.S. Appl. No. 14/699,567, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler and Method for Counting Doses.".
Entire patent prosecution history of U.S. Appl. No. 14/699,578, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having a Bore !and Shaft Arrangement.".
Entire patent prosecution history of U.S. Appl. No. 14/699,584, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having an Antireverse Rotation Actuator.".
Entire patent prosecution history of U.S. Appl. No., 14/713,612, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/713,620, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/713,643, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 211.8.
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 212.6.
First Examination Report of counterpart New Zealand Patent Application No. 603466, dated Jul. 1, 2013.
Office Action issued by the Israel Patent Office on Jul. 3, 2017 in reference to Israel Patent Application No. 247396, 3 pages.
Office Action issued by the Israel Patent Office on Jul. 27, 2017 in reference to Israel Patent Application No. 247402, 4 pages.

* cited by examiner

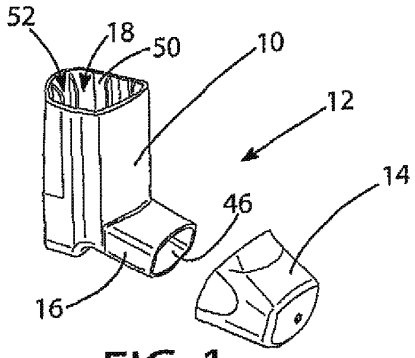


FIG. 1

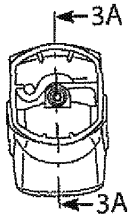


FIG. 2

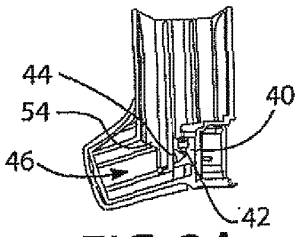


FIG. 3A

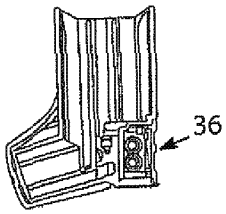


FIG. 3B

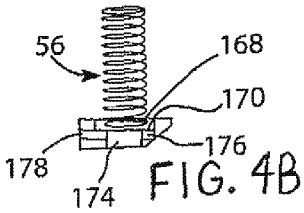


FIG. 4B

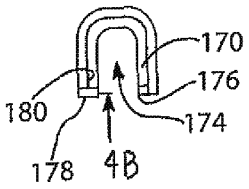


FIG. 4C

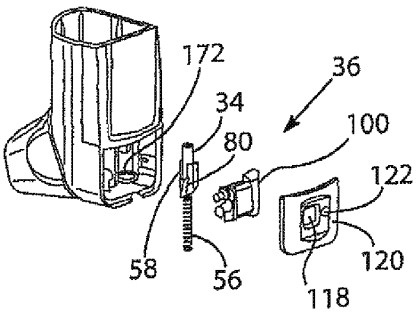


FIG. 4A

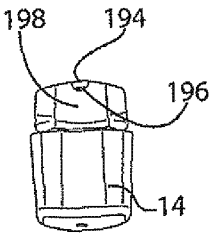


FIG. 5

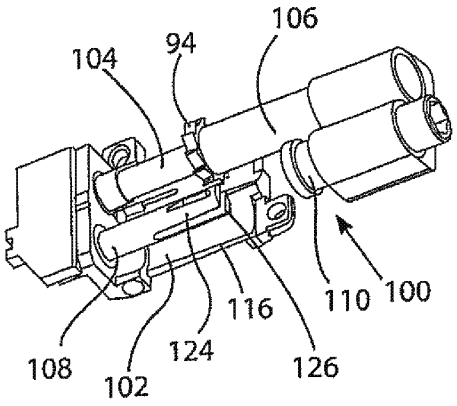


FIG. 6A

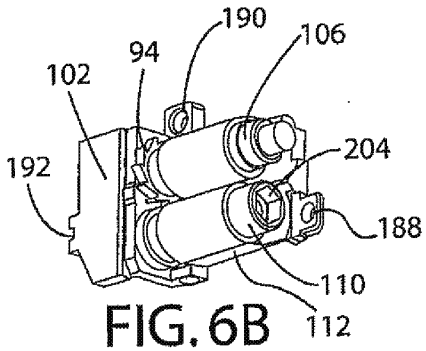


FIG. 6B

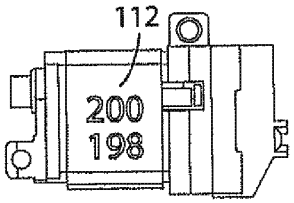


FIG. 6C

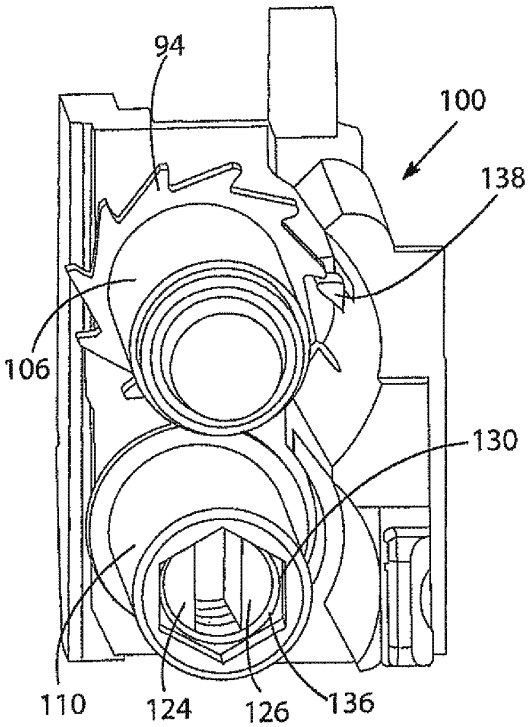


FIG. 6D

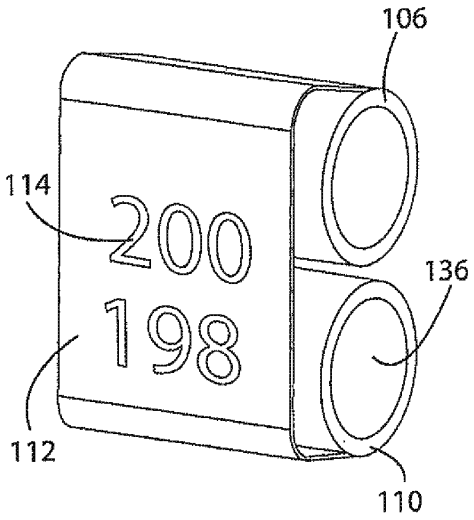


FIG. 6E

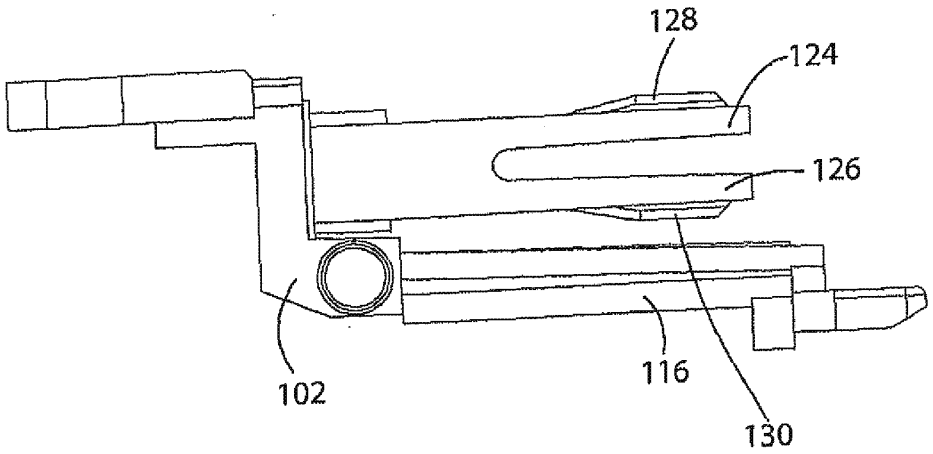


FIG. 6F

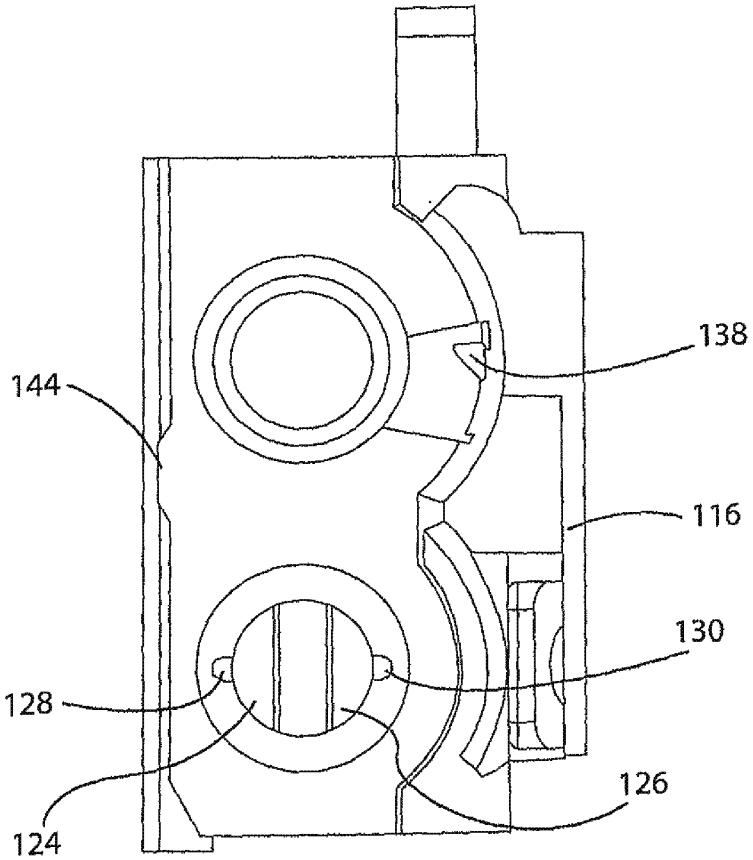


FIG. 6G

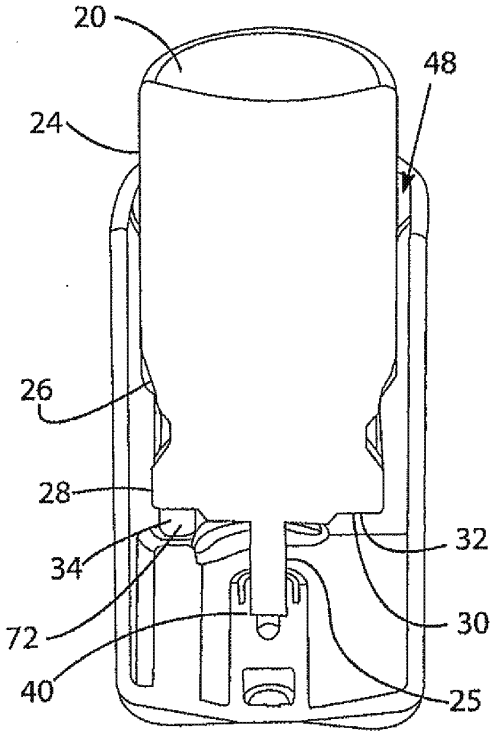


FIG. 7A

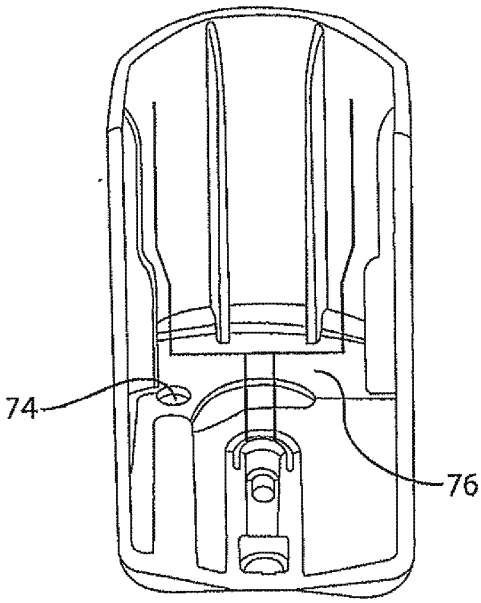


FIG. 7B

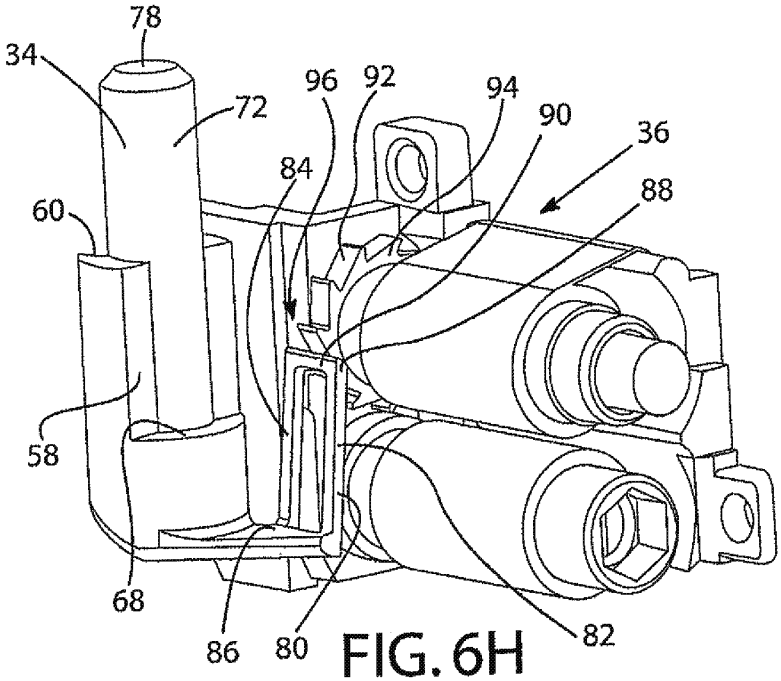


FIG. 6H

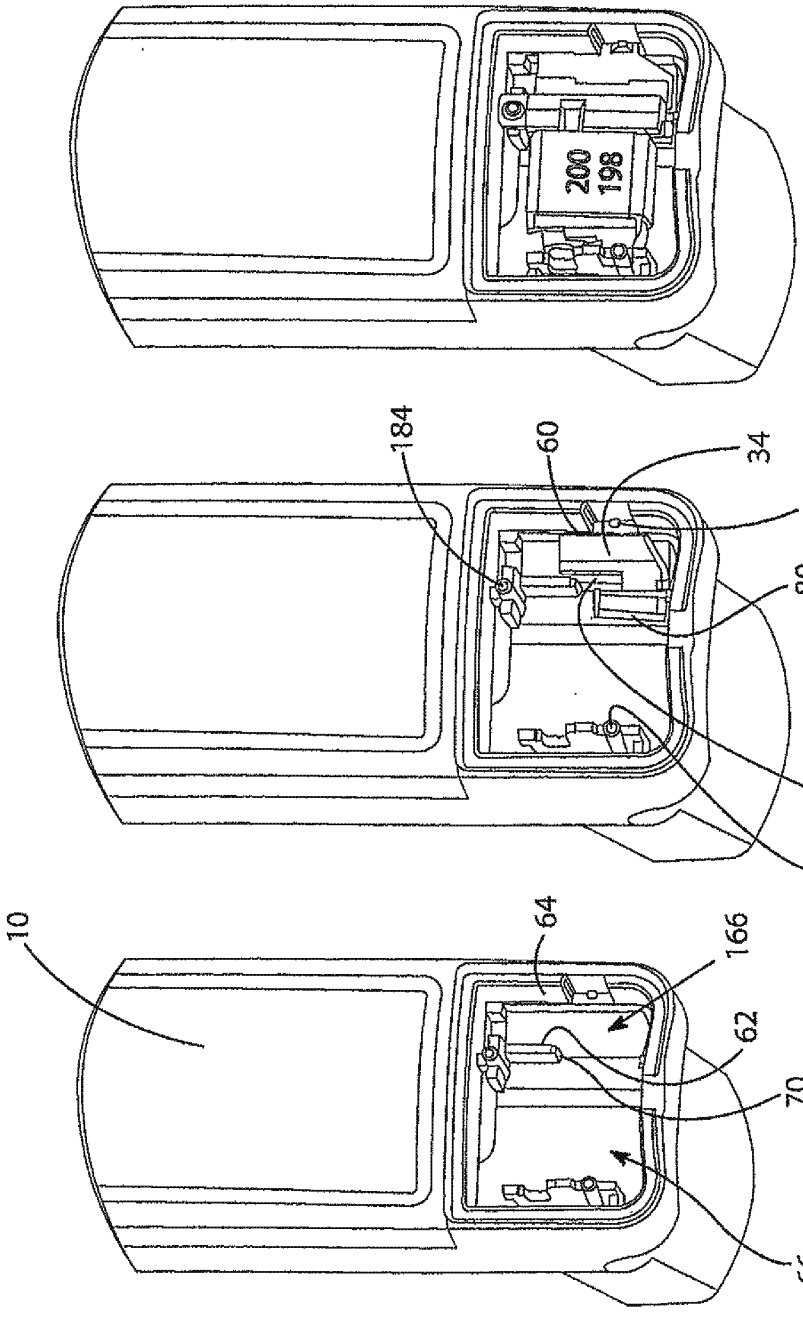


FIG. 8C

FIG. 8B

FIG. 8A

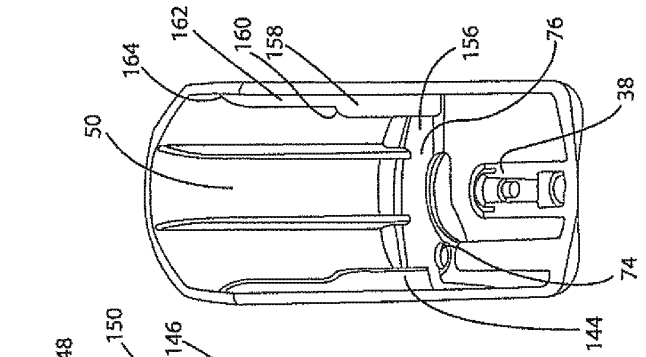


FIG. 7C

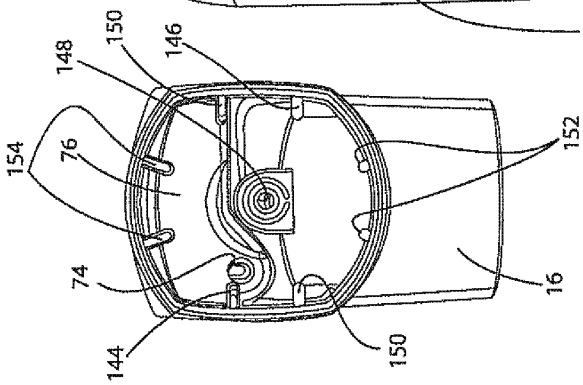


FIG. 7D

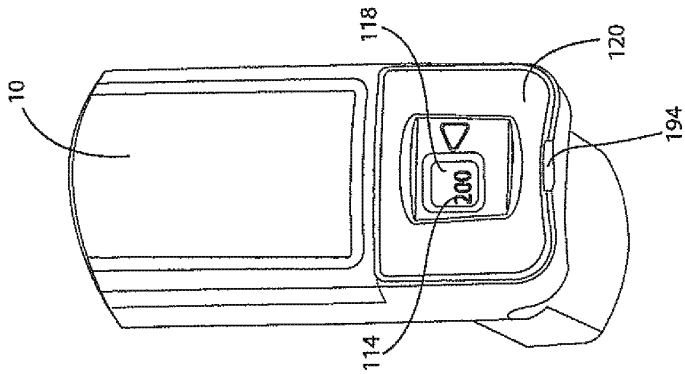


FIG. 8D

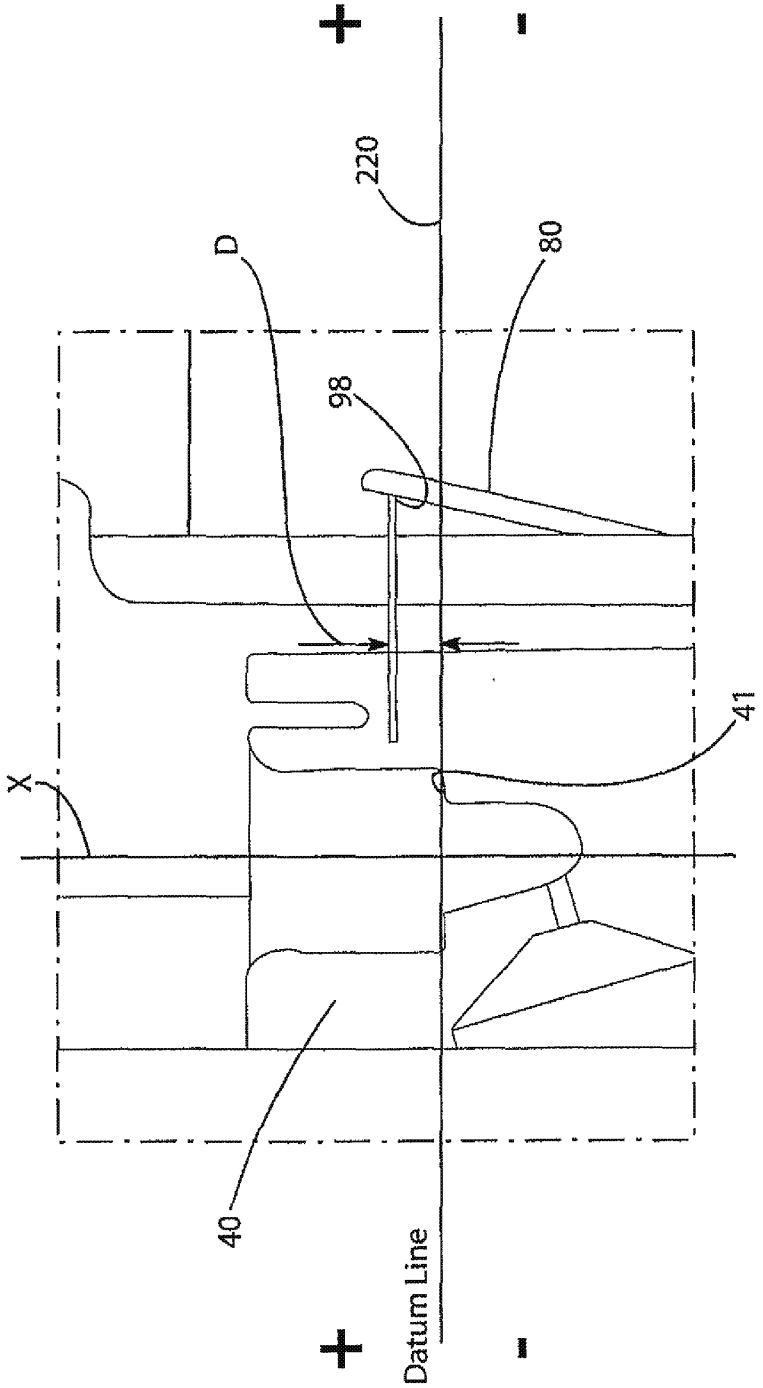


FIG. 9

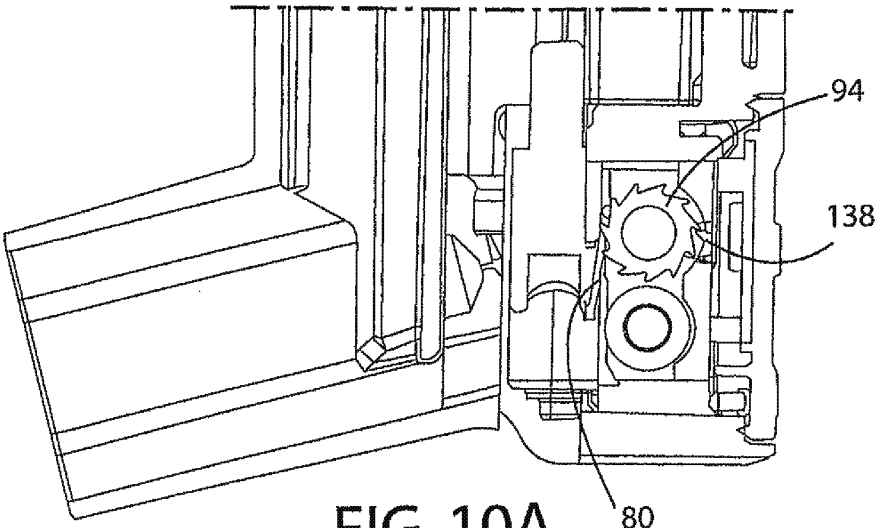


FIG. 10A

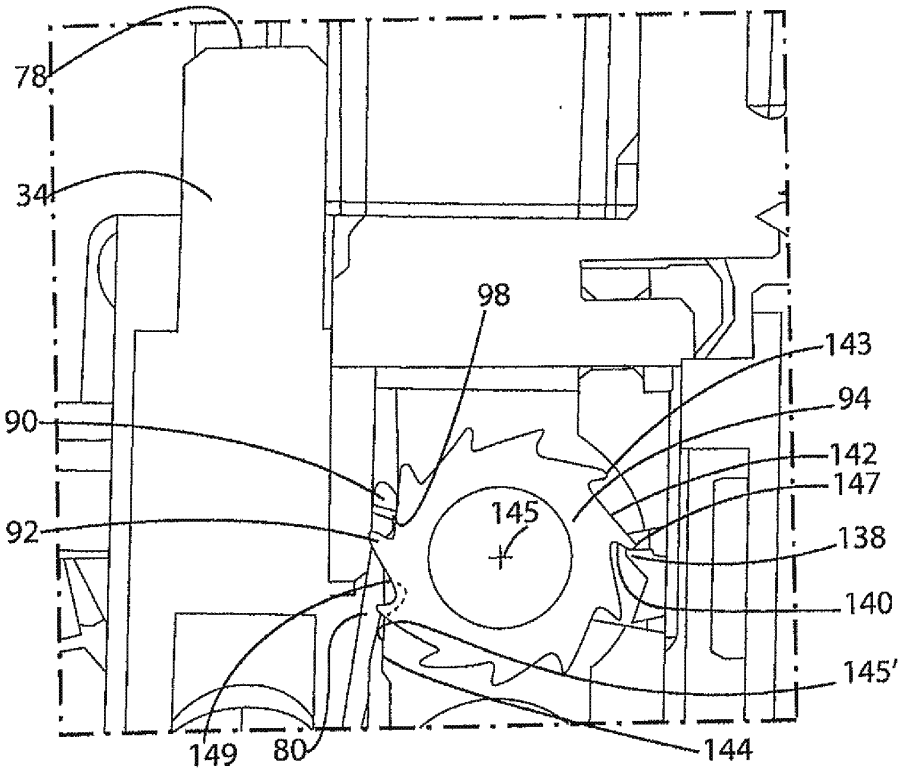


FIG. 10B

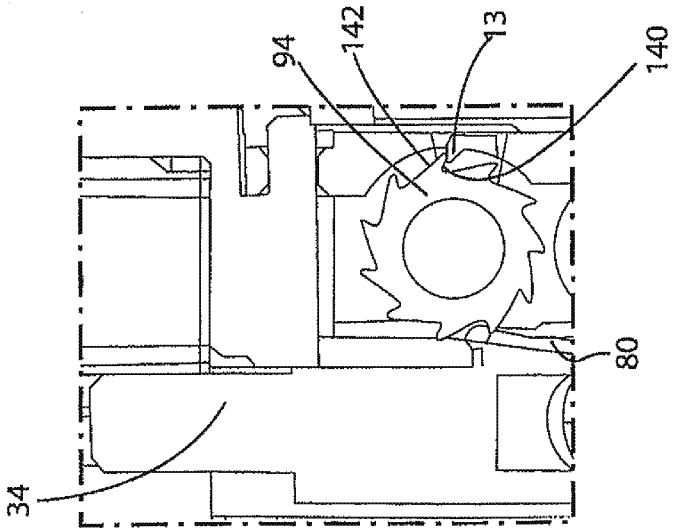


FIG. 10E

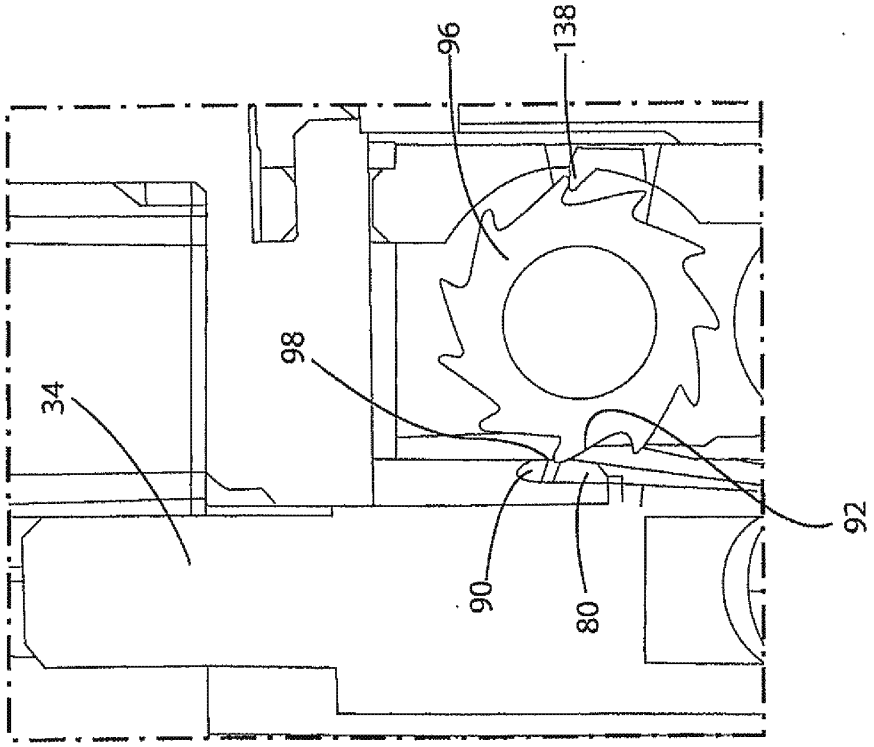


FIG. 10C

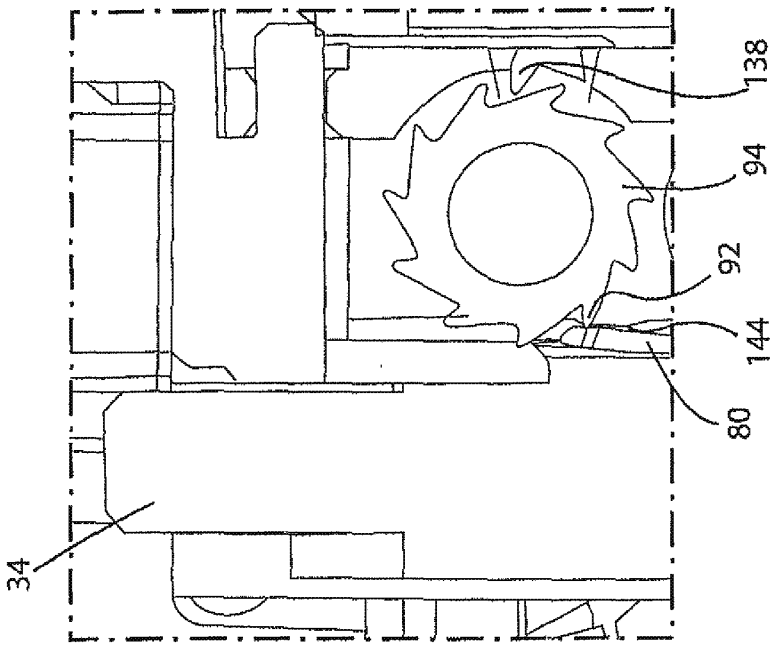


FIG. 10F

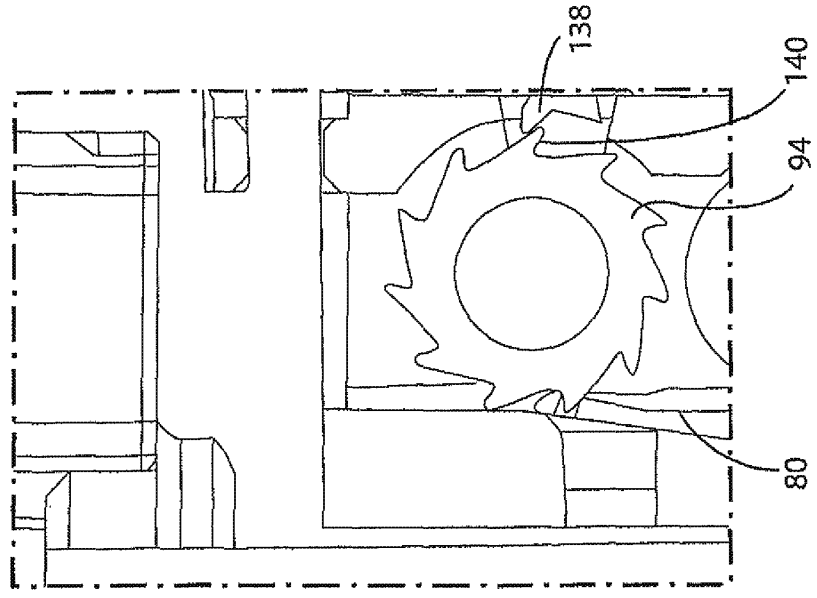


FIG. 10D

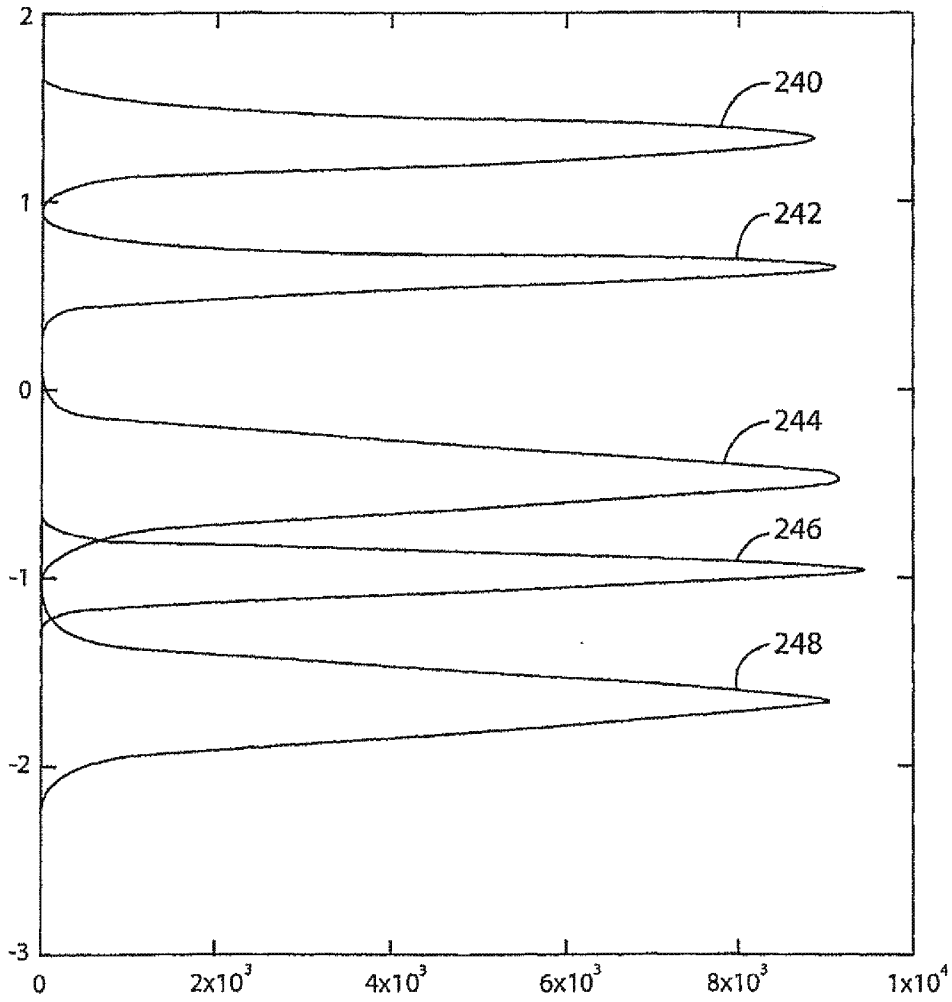

2
1
0
-1
-2
-3
0
2x10^3
4x10^3
6x10^3
8x10^3
1x10^4
240
242
244
246
248

FIG. 11

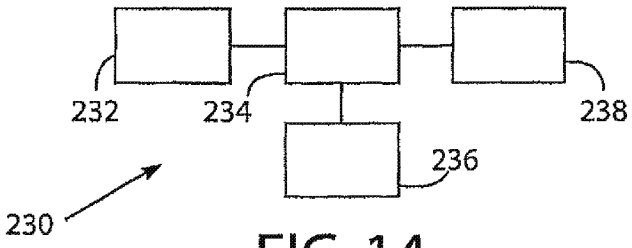

232
234
238
236
230

FIG. 14

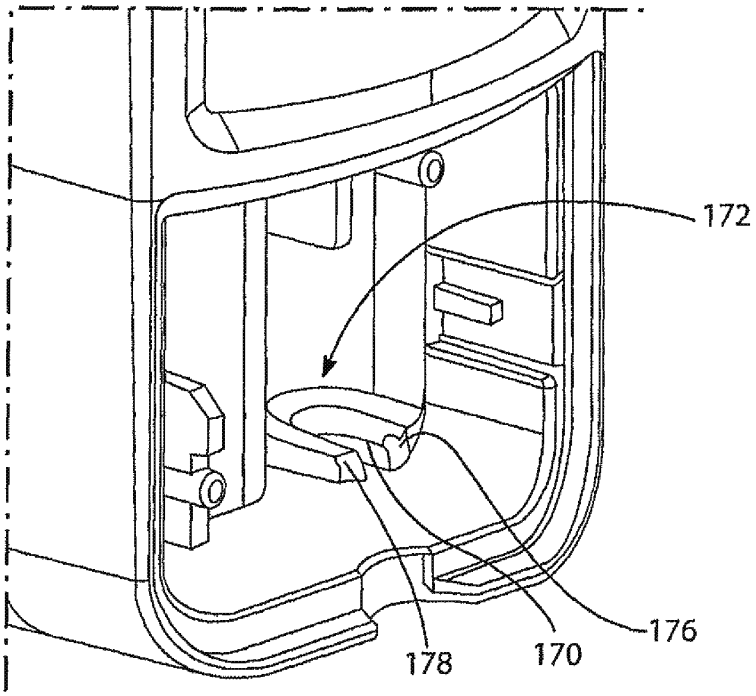


FIG. 12

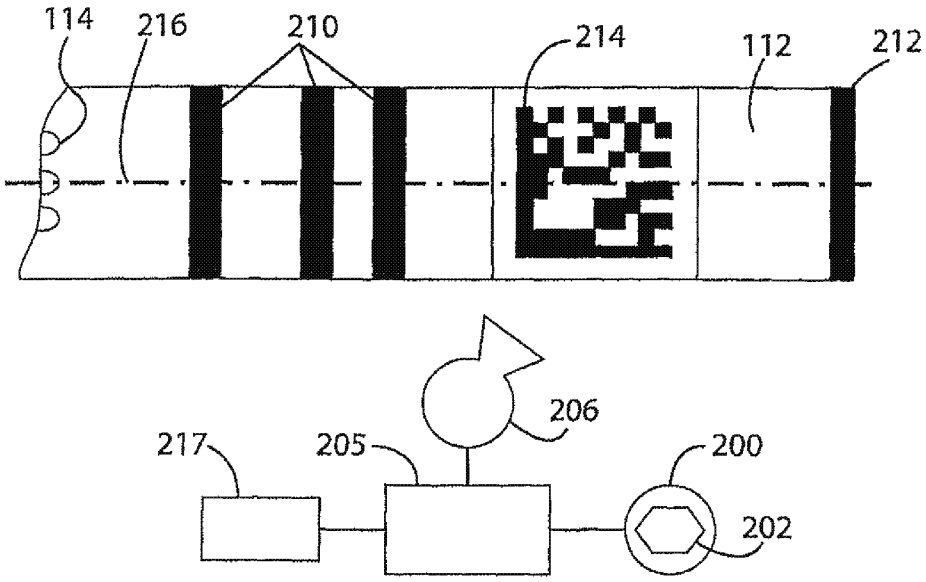


FIG. 13

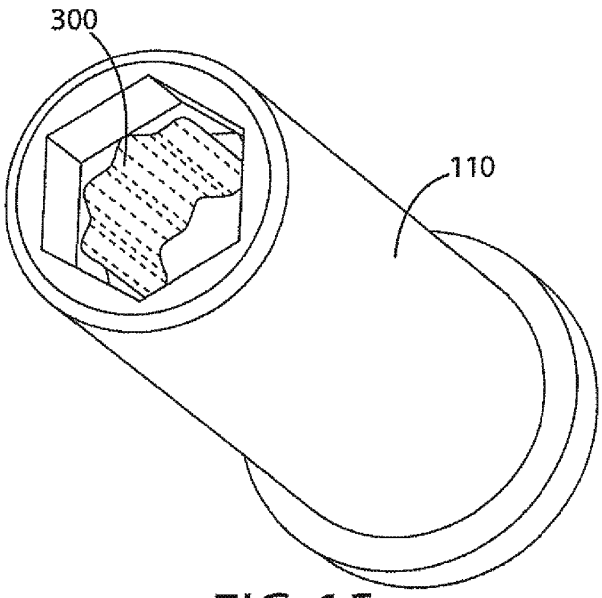


FIG. 15

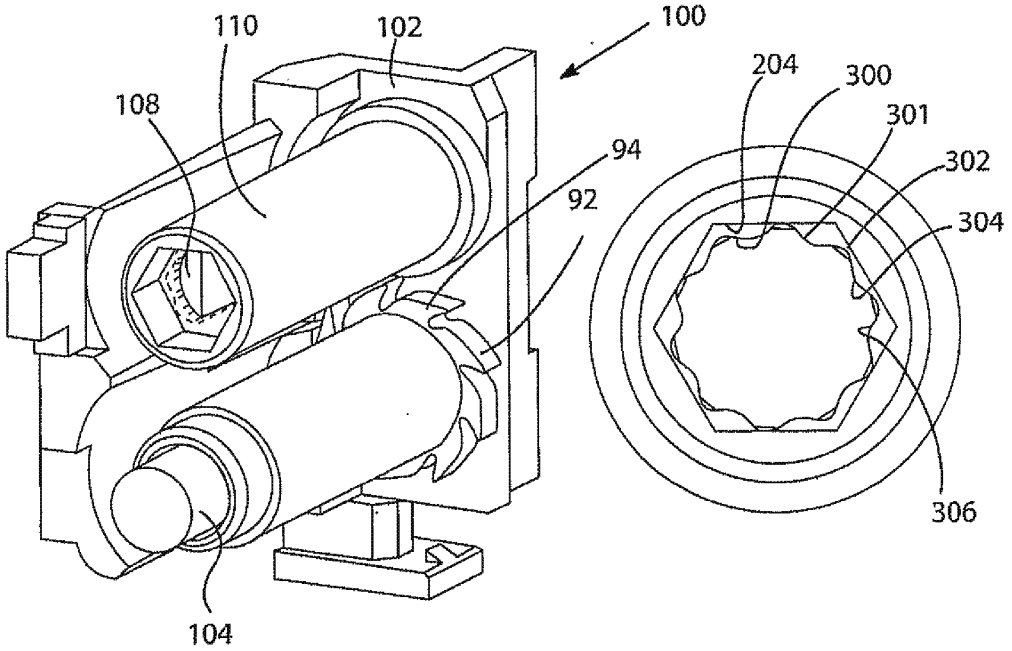


FIG. 20

FIG. 16

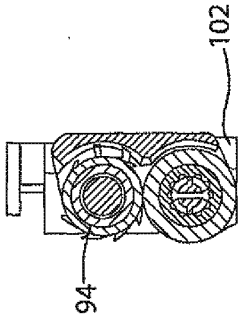


FIG. 19A

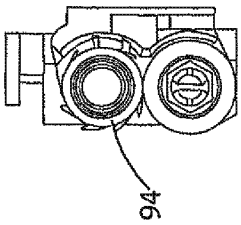


FIG. 19B

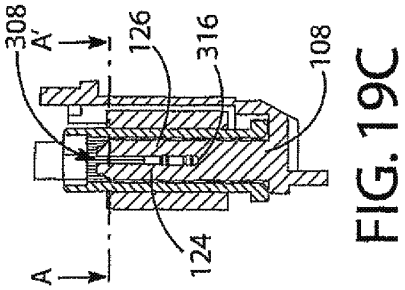


FIG. 19C

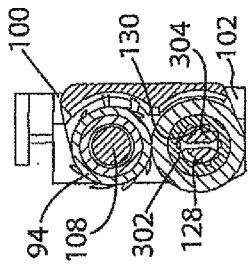


FIG. 18A

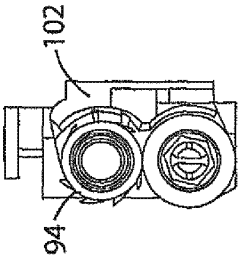


FIG. 18B

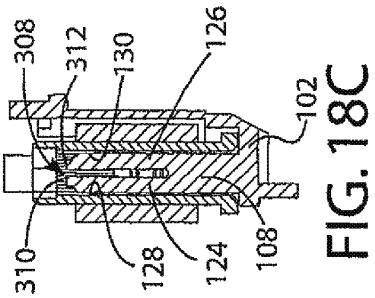


FIG. 18C

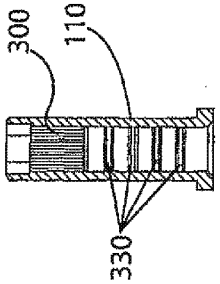


FIG. 17

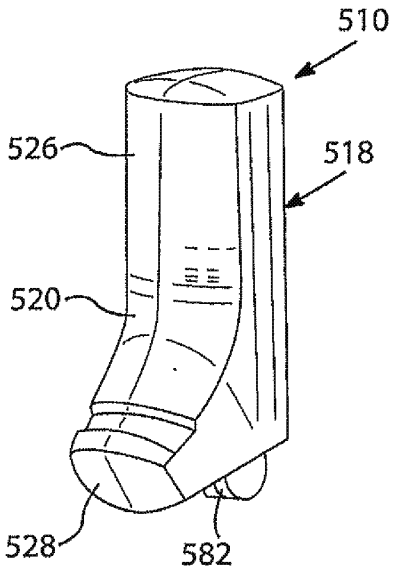

510
526
518
520
528
582

FIG. 21

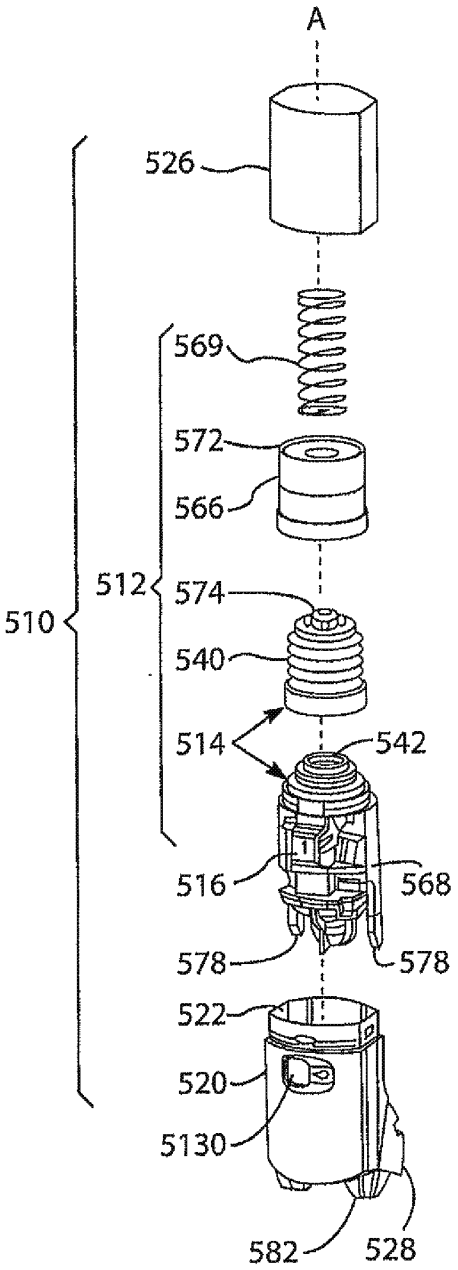

A
526
569
572
566
512
574
510
540
514
542
516
568
578
578
522
520
5130
582
528

FIG. 22

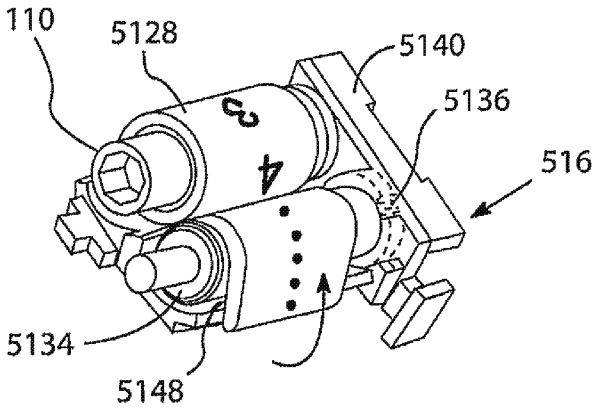

110
5128
5140
5136
516
5134
5148

FIG. 23

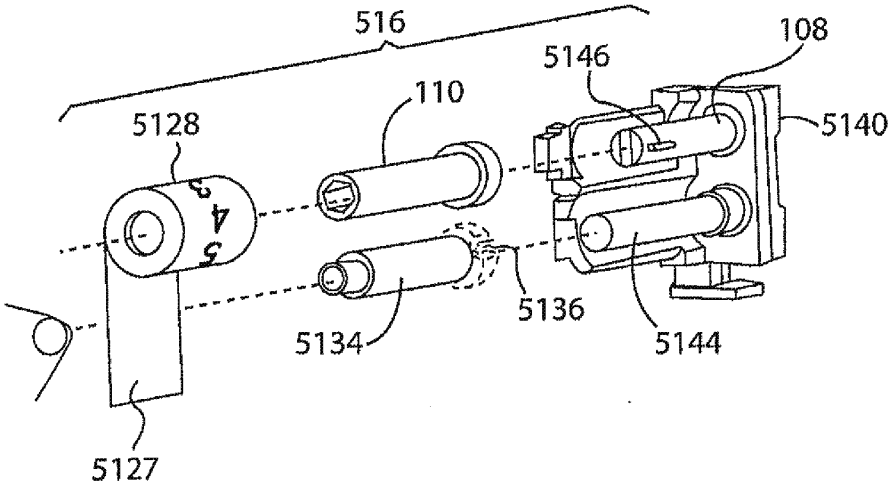

516
108
5146
110
5128
5140
5136
5134
5144
5127

FIG. 24

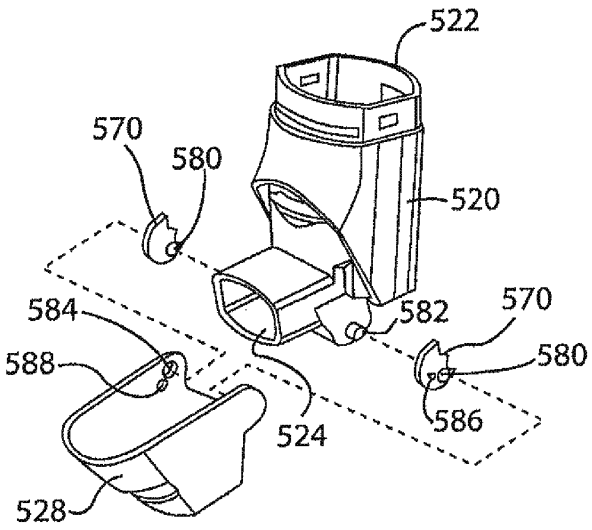


FIG. 25

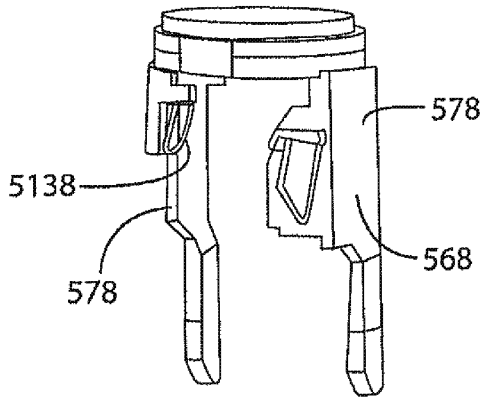


FIG. 26

DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation patent application of U.S. Non-Provisional patent application Ser. No. 14/103,324, filed Dec. 11, 2013, which is a divisional patent application of U.S. Non-Provisional patent application Ser. No. 13/110,532, filed May 18, 2011, now U.S. Pat. No. 8,978,966, issued Mar. 17, 2015, which claims priority to U.S. Provisional Patent Application No. 61/345,763, filed May 18, 2010, and U.S. Provisional Patent Application No. 61/417,659, filed Nov. 29, 2010, each of which is incorporated herein by reference in its entirety for any and all purposes.

FIELD OF THE INVENTION

The present invention relates to dose counters for inhalers, inhalers and methods of assembly thereof. The invention is particularly applicable to metered dose inhalers including dry power medicament inhalers, breath actuated inhalers and manually operated metered dose medicament inhalers.

BACKGROUND OF THE INVENTION

Metered dose inhalers can comprise a medicament-containing pressurised canister containing a mixture of active drug and propellant. Such canisters are usually formed from a deep-dawn aluminium cup having a crimped lid which carries a metering valve assembly. The metering valve assembly is provided with a protruding valve stem which, in use is inserted as a push fit into a stem block in an actuator body of an inhaler having a drug delivery outlet. In order to actuate a manually operable inhaler, the user applies by hand a compressive force to a closed end of the canister and the internal components of the metering valve assembly are spring loaded so that a compressive force of approximately 15 to 30 N is required to activate the device in some typical circumstances.

In response to this compressive force the canister moves axially with respect to the valve stem and the axial movement is sufficient to actuate the metering valve and cause a metered quantity of the drug and the propellant to be expelled through the valve stem. This is then released into a mouthpiece of the inhaler via a nozzle in the stem block, such that a user inhaling through the outlet of the inhaler will receive a dose of the drug.

A drawback of self-administration from an inhaler is that it is difficult to determine how much active drug and/or propellant are left in the inhaler, if any, especially of the active drug and this is potentially hazardous for the user since dosing becomes unreliable and backup devices not always available.

Inhalers incorporating dose counters have therefore become known.

WO 98/028033 discloses an inhaler having a ratchet mechanism for driving a tape drive dose counter. A shaft onto which tape is wound has a friction clutch or spring for restraining the shaft against reverse rotation.

EP-A-1486227 discloses an inhaler for dry powered medicament having a ratchet mechanism for a tape dose counter which is operated when a mouthpiece of the inhaler is closed. Due to the way in which the mouthpiece is opened and closed, and actuation pawl of the device which is mounted on a yoke, travels a known long stroke of consistent length as the mouthpiece is opened and closed.

WO 2008/119552 discloses a metered-dose inhaler which is suitable for breath-operated applications and operates with a known and constant canister stroke length of 3.04 mm+/−0.255 mm. A stock bobbin of the counter, from which a tape is unwound, rotates on a shaft having a split pin intended to hold the stock bobbin taut. However, some dose counters do not keep a particularly reliable count, such as if they are dropped onto a hard surface.

More recently, it has become desirable to improve dose counters further and, in particular, it is felt that it would be useful to provide extremely accurate dose counters for manually-operated canister-type metered dose inhalers. Unfortunately, in these inhalers, it has been found in the course of making the present invention that the stroke length of the canister is to a very large extent controlled on each dose operation by the user, and by hand. Therefore, the stroke length is highly variable and it is found to be extremely difficult to provide a highly reliable dose counter for these applications. The dose counter must not count a dose when the canister has not fired since this might wrongly indicate to the user that a dose has been applied and if done repeatedly the user would throw away the canister or whole device before it is really time to change the device due to the active drug and propellant reaching a set minimum. Additionally, the canister must not fire without the dose counter counting because the user may then apply another dose thinking that the canister has not fired, and if this is done repeatedly the active drug and/or propellant may run out while the user thinks the device is still suitable for use according to the counter. It has also been found to be fairly difficult to assembly some known inhaler devices and the dose counters therefor. Additionally, it is felt desirable to improve upon inhalers by making them easily usable after they have been washed with water.

The present invention aims to alleviate at least to a certain extent one or more of the problems of the prior art.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a counter display arranged to indicate dosage information, a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

The regulator is advantageous in that it helps prevent unwanted motion of the counter display if the counter is dropped.

According to a further aspect of the present invention, the regulator provides a resistance force of greater than 0.1 N against movement of the counter display. According to still a further aspect of the present invention, the resistance force is greater than 0.3 N. According to yet a further aspect of the present invention, the resistance force is from 0.3 to 0.4 N.

Preferably, the counter comprises a tape.

Preferably, the tape has dose counter indicia displayed thereon. The first station may comprise a region of the dose counter where tape is held which is located before a display location, such as a display window, for the counter indicia.

The first station may comprise a first shaft, the tape being arranged on the first shaft and to unwind therefrom upon movement of the counter display.

The first shaft may be mounted for rotation relative to a substantially rotationally fixed element of the dose counter.

The regulator may comprise at least one projection which is arranged on one of the first shaft and the substantially rotationally fixed element and to engage incrementally with one or more formations on the other of the first shaft and the substantially rotationally fixed element.

At least two said projections may be provided. Exactly two said projections maybe provided.

Each projection may comprise a radiused surface.

The at least one projection may be located on the substantially fixed element which may comprise a fixed shaft which is fixed to a main body of the dose counter, the first shaft being rotationally mounted to the fixed shaft.

Preferably, the fixed shaft has at least two resiliently flexible legs (or forks). Each leg may have at least one said projection formed in an outwardly facing direction thereon, said one or more formations being formed on an inwardly facing engagement surface of the first shaft, said at least one projection being arranged to resiliently engage said one or more formations. Preferably, a series of said formations are provided. An even number of said formations may be provided. Eight to twelve of said formations may be provided. In one embodiment, ten said formations are provided.

Each said formation may comprise a concavity formed on an engagement surface. Each concavity may comprise a radiused surface wall portion which preferably merges on at least one side thereof into a flat wall portion surface. The engagement surface may include a series of said concavities, and convex wall portions of the engagement surface may be formed between each adjacent two said concavities, each said convex wall portion comprising a convex radiused wall portion.

Each convex radiused wall portion of each convex wall portion may be connected by said flat wall portion surfaces to each adjacent concavity.

The fixed shaft may comprise a split pin with fork legs and each projection may be located on a said fork leg.

The first shaft may comprise a substantially hollow bobbin.

Said at least one formation may be located on an inner surface of the bobbin. In other embodiments it may be located on an outer surface thereof. Said engagement surface may extend partially along said bobbin, a remainder of the respective inner or outer surface having a generally smooth journal portion along at least a portion thereof.

The drive system may comprise a tooth ratchet wheel arranged to act upon a second shaft which is located at the second station, the second shaft being rotatable to wind the tape onto the second shaft.

The second shaft may be located on a main body of the dose counter spaced from and parallel to the first shaft.

The ratchet wheel may be fixed to the second shaft is arranged to rotate therewith. The ratchet wheel may be secured to an end of the second shaft and aligned coaxially with the second shaft.

The dose counter may include anti-back drive system which is arranged to restrict motion of the second shaft. The anti-back drive system may include a substantially fixed tooth arranged to act upon teeth of the ratchet wheel.

According to a further aspect of the present invention, a dose counter includes an anti-back drive system which is arranged to restrict motion of the second shaft in a tape winding direction.

According to a further aspect of the present invention there is provided a shaft for holding counter tape in a dose counter for an inhaler, the shaft having an engagement surface including incrementally spaced formations located around a periphery thereof, the formations comprising a series of curved concavities and convex portions.

The shaft may comprise a hollow bobbin.

The engagement surface may be a generally cylindrical inwardly directed surface.

The engagement surface may include a flat surface wall portion joining each concavity and convex wall portion.

Each concavity may comprise a radiused wall portion.

Each convex wall portion may comprise a radiused wall portion.

Said concavities may be regularly spaced around a longitudinal axis of the shaft.

Said convex wall portions may be regularly spaced around a longitudinal axis of the shaft.

In some embodiments there may be from eight to twelve said concavities and/or convex wall portions regularly spaced around a longitudinal axis thereof.

One embodiment includes ten said concavities and/or convex wall portions regularly spaced around a longitudinal axis of the shaft.

According to a further aspect of the present invention there is provided a shaft and counter tape assembly for use in a dose counter for an inhaler, the assembly comprising a rotatable shaft and a counter tape which is wound around the shaft and is adapted to unwind therefrom upon inhaler actuation, the shaft having an engagement surface which includes incrementally spaced formations located around a periphery thereof.

According to a further aspect of the present invention there is provided an inhaler for the inhalation of medication and the like, the inhaler including a dose counter as in the first aspect of the present invention.

A preferred construction consists of a manually operated metered dose inhaler including a dose counter chamber including a dose display tape driven by a ratchet wheel which is driven in turn by an actuator pawl actuated by movement of a canister, the tape unwinding from a stock bobbin during use of the inhaler, a rotation regulator being provided for the stock bobbin and comprising a wavelike engagement surface with concavities which engage against control elements in the form of protrusions on resilient forks of a split pin thereby permitting incremental unwinding of the stock bobbin yet resisting excessive rotation if the inhaler is dropped onto a hard surface.

According to another aspect of the present invention there is provided a dose counter for a metered dose inhaler having a body arranged to retain a medicament canister of predetermined configuration for movement of the canister relative thereto; the dose counter comprising: an incremental counting system for counting doses, the incremental counting system having a main body, an actuator arranged to be driven in response to canister motion and to drive an incremental output member in response to canister motion, the actuator and incremental output member being configured to have predetermined canister fire and count configurations in a canister fire sequence, the canister fire configuration being determined by a position of the actuator relative to a datum at which the canister fires medicament and the count configuration being determined by a position of the actuator relative to the datum at which the incremental count system makes an incremental count, wherein the actuator is

arranged to reach a position thereof in the count configuration at or after a position thereof in the canister fire configuration.

This arrangement has been found to be highly advantageous since it provides an extremely accurate dose counter which is suitable for use with manually operated metered dose inhalers. It has been found that dose counters with these features have a failure rate of less than 50 failed counts per million full canister activation depressions. It has been found in the course of making the present invention that highly reliable counting can be achieved with the dose counter counting at or soon after the point at which the canister fires. It has been is covered by the present inventors that momentum and motion involved in firing the canister, and in some embodiments a slight reduction in canister back pressure on the user at the time of canister firing, can very reliably result in additional further motion past the count point.

The actuator and incremental counting system may be arranged such that the actuator is displaced less than 1 mm, typically 0.25 to 0.75 mm, more preferably about 0.4 to 0.6 mm, relative to the body between its location in the count and fire configurations, about 0.48 mm being preferred. The canister, which can move substantially in line with the actuator, can reliably move this additional distance so as to achieve very reliable counting.

The incremental count system may comprise a ratchet mechanism and the incremental output member may comprise a ratchet wheel having a plurality of circumferentially spaced teeth arranged to engage the actuator.

The actuator may comprise an actuator pawl arranged to engage on teeth of the ratchet wheel. The actuator pawl may be arranged to be connected to or integral with an actuator pin arranged to engage and be depressed by a medicament canister bottom flange. The actuator pawl may be generally U-shaped having two parallel arms arranged to pull on a central pawl member arranged substantially perpendicular thereto. This provides a very reliable actuator pawl which can reliably pull on the teeth of the ratchet wheel.

The incremental count system may include a tape counter having tape with incremental dose indicia located thereon, the tape being positioned on a tape stock bobbin and being arranged to unwind therefrom.

The actuator and incremental output member may be arranged to provide a start configuration at which the actuator is spaced from the ratchet output member, a reset configuration at which the actuator is brought into engagement with the incremental output member during a canister fire sequence, and an end configuration at which the actuator disengages from the ratchet output during a canister fire sequence.

The actuator may be arranged to be located about 1.5 to 2.0 mm, from its location in the fire configuration, when in the start configuration, about 1.80 mm being preferred.

The actuator may be arranged to be located about 1.0 to 1.2 mm, from its location in the fire configuration, when in the reset configuration, about 1.11 mm being preferred.

The actuator may be arranged to be located about 1.1 to 1.3 mm, from its location in the fire configuration, when in the end configuration, about 1.18 mm being preferred.

These arrangements provide extremely reliable dose counting, especially with manually operated canister type metered dose inhalers.

The main body may include a formation for forcing the actuator to disengage from the incremental output member when the actuator is moved past the end configuration. The formation may comprise a bumped up portion of an otherwise generally straight surface against which the actuator engages and along which it is arranged to slide during a canister firing sequence.

The dose counter may include a counter pawl, the counter pawl having a tooth arranged to engage the incremental output member, the tooth and incremental output member being arranged to permit one way only incremental relative motion therebetween. When the incremental output member comprises a ratchet wheel, the tooth can therefore serve as an anti-back drive tooth for the ratchet wheel, thereby permitting only one way motion or rotation thereof.

The counter pawl may be substantially fixedly mounted on the main body of the incremental count system and the counter pawl may be arranged to be capable of repeatedly engaging equi-spaced teeth of the incremental output member in anti-back drive interlock configurations as the counter is operated. The counter pawl may be positioned so that the incremental output member is halfway, or substantially halfway moved from one anti-back drive interlock configuration to the next when the actuator and incremental output member are in the end configuration thereof. This is highly advantageous in that it minimises the risk of double counting or non-counting by the dose counter.

According to a further aspect of the invention there is provided an inhaler comprising a main body arranged to retain a medicament canister of predetermined configuration and a dose counter mounted in the main body.

The inhaler main body may include a canister receiving portion and a separate counter chamber, the dose counter being located within the main body thereof, the incremental output member and actuator thereof inside the counter chamber, the main body of the inhaler having wall surfaces separating the canister-receiving portion and the counter chamber, the wall surfaces being provided with a communication aperture, an actuation member extending through the communication aperture to transmit canister motion to the actuator.

According to a further aspect of the present invention there is a provided an inhaler for metered dose inhalation, the inhaler comprising a main body having a canister housing arranged to retain a medicament canister for motion therein, and a dose counter, the dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of a medicament canister, wherein the canister housing has an inner wall, and a first inner wall canister support formation located directly adjacent the actuation member.

This is highly advantageous in that the first inner wall canister support formation can prevent a canister from rocking too much relative to the main body of the inhaler. Since the canister may operate the actuation member of the dose counter, this substantially improves dose counting and avoids counter errors.

The canister housing may have a longitudinal axis which passes through a central outlet port thereof, the central outlet port being arranged to mate with an outer canister fire stem of a medicament canister, the inner wall canister support formation, the actuation member and the outlet port lying in a common plane coincident with the longitudinal axis. Accordingly, this construction may prevent the canister from rocking towards the position of the dose counter actuation member, thereby minimising errors in counting.

The canister housing may have a further inner canister wall support formation located on the inner wall opposite, or substantially opposite, the actuation member. Accordingly, the canister may be supported against rocking motion away from the actuator member so as to minimise count errors.

The canister housing may be generally straight and tubular and may have an arrangement in which each said inner wall support formation comprises a rail extending longitudinally along the inner wall.

Each said rail may be stepped, in that it may have a first portion located towards a medicine outlet end or stem block of the canister housing which extends inwardly a first distance from a main surface of the inner wall and a second portion located toward an opposite end of the canister chamber which extends inwardly a second, smaller distance from the main surface of the inner wall. This may therefore enable easy insertion of a canister into the canister housing such that a canister can be lined up gradually in step wise function as it is inserted into the canister housing.

The inhaler may include additional canister support rails which are spaced around an inner periphery of the inner wall of the canister housing and which extend longitudinally therealong.

At least one of the additional rails may extend a constant distance inwardly from the main surface of the inner wall.

At least one of the additional rails may be formed with a similar configuration to the first inner wall canister support formation.

The dose counter may, apart from said at least a portion of the actuation member, be located in a counter chamber separate from the canister housing, the actuation member comprising a pin extending through an aperture in a wall which separates the counter chamber and the canister housing.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicaments having: a body for retaining a medicament store; the body including a dose counter, the dose counter having a moveable actuator and a return spring for the actuator, the return spring having a generally cylindrical and annular end; the body having a support formation therein for supporting said end of the return spring, the support formation comprising a shelf onto which said end is engageable and a recess below the shelf.

This shelf and recess arrangement is highly advantageous since it allows a tool (such as manual or mechanical tweezers) to be used to place the return spring of the actuator onto the shelf with the tool then being withdrawn at least partially via the recess.

The shelf may be U-shaped.

The support formation may include a U-shaped upstanding wall extending around the U-shaped shelf, the shelf and upstanding wall thereby forming a step and riser of a stepped arrangement.

The recess below the shelf my also be U-shaped.

At least one chamfered surface may be provided at an entrance to the shelf. This may assist in inserting the actuator and return spring into position.

A further aspect of the invention provides a method of assembly of an inhaler which includes the step of locating said end of said spring on the shelf with an assembly tool and then withdrawing the assembly tool at least partly via the recess. This assembly method is highly advantageous compared to prior art methods in which spring insertion has been difficult and in which withdrawal of the tool has sometimes accidentally withdrawn the spring again.

The cylindrical and annular end of the spring may be movable in a direction transverse to its cylindrical extent into the shelf while being located thereon.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament, the inhaler having a body for retaining a medicament store; and a dose counter, the dose counter having a moveable actuator and a chassis mounted on the body; the chassis being heat staked in position on the body. This is be highly advantageous in that the chassis can be very accurately positioned and held firmly in place, thereby further improving counting accuracy compared to prior art arrangements in which some movement of the chassis relative to the body may be tolerated in snap-fit connections.

The chassis may have at least one of a pin or aperture heat staked to a respective aperture or pin of the body.

The chassis may have a ratchet counter output member mounted thereon.

The ratchet counter output member may comprise a ratchet wheel arranged to reel in incrementally a dose meter tape having a dosage indicia located thereon.

According to a further aspect of the present invention there is provided a method of assembling an inhaler including the step of heat staking the chassis onto the body. The step of heat staking is highly advantageous in fixedly positioning the chassis onto the body in order to achieve highly accurate dose counting in the assembled inhaler.

The method of assembly may include mounting a spring-returned ratchet actuator in the body before heat staking the chassis in place. The method of assembly may include pre-assembling the chassis with a dose meter tape prior to the step of heat staking the chassis in place. The method of assembly may include attaching a dose meter cover onto the body after the heat staking step. The cover may be welded onto the body or may in some embodiments be glued or otherwise attached in place.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament and having a body, the body have a main part thereof for retaining a medicament store; and a dose counter, the dose counter being located in a dose counter chamber of the body which is separated from the main part of the body, the dose counter chamber of the body having a dosage display and being perforated so as to permit the evaporation of water or aqueous matter in the dose counter chamber into the atmosphere.

This is high advantageous since it enables the inhaler to be thoroughly washed and the dose counting chamber can thereafter dry out fully.

The display may comprise a mechanical counter display inside the dose counter chamber and a window for viewing the mechanical counter display. The mechanical counter display may comprise a tape. The perforated dose counter chamber may therefore enable reliable washing of the inhaler, if desired by the user, and may therefore dry out without the display window misting up.

The dose counter chamber may be perforated by a drain hole formed through an outer hole of the body. The drain hole may be located at a bottom portion of the body of the inhaler, thereby enabling full draining of the inhaler to be encouraged after washing when the inhaler is brought into an upright position.

According to a further aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a display tape arranged to be incrementally driven from a tape stock bobbin onto an incremental tape take-up drive shaft, the bobbin having an internal bore supported by and for rotation about a support shaft, at least one of the bore and support shaft having a protrusion which is resiliently biased into frictional engagement with the other of the bore and support shaft with longitudinally extending mutual frictional interaction. This arrangement may provide good friction for the bobbin, thereby improving tape counter

display accuracy and preventing the bobbin from unwinding undesirably for example if the inhaler is accidentally dropped.

The support shaft may be forked and resilient for resiliently biasing the support shaft and bore into frictional engagement.

The support shaft may have two forks, or more in some cases, each having a radially extending protrusion having a friction edge extending therealong parallel to a longitudinal axis of the support shaft for frictionally engaging the bore of the support shaft with longitudinally extending frictional interaction therebetween.

The bore may be a smooth circularly cylindrical or substantially cylindrical bore.

Each of the above inhalers in accordance with aspects of the present invention may have a medicament canister mounted thereto.

The canister may comprise a pressurised metered dose canister having a reciprocally movable stem extending therefrom and movable into a main canister portion thereof for releasing a metered dose of medicament under pressure, for example by operating a metered dose valve inside the canister body. The canister may be operable by pressing by hand on the main canister body.

In cases in which one or more support rails or inner wall support formations are provided, the canister may at all times when within the canister chamber have a clearance of about 0.25 to 0.35 mm from the first inner wall support formation. The clearance may be almost exactly 0.3 mm. This clearance which may apply to the canister body itself or to the canister once a label has been applied, is enough to allow smooth motion of the canister in the inhaler while at the same time preventing substantial rocking of the canister which could result in inaccurate counting by a dose counter of the inhaler, especially when lower face of the canister is arranged to engage an actuator member of the dose counter for counting purposes.

According to a further aspect of the invention, a method of assembling a dose counter for an inhaler comprises the steps of providing a tape with dosing indicia thereon; providing tape positioning indicia on the tape; and stowing the tape while monitoring for the tape positioning indicia with a sensor. The method advantageously permits efficient and accurate stowing of the tape, e.g. by winding.

The dosing indicia may be provided as numbers, the tape positioning indicia may be provided as one or more lines across the tape. The stowing step comprises winding the tape onto a bobbin or shaft, and, optionally, stopping winding when the positioning indicia are in a predetermined position. The tape may be provided with pixelated indicia at a position spaced along the tape from the positioning indicia. The tape may also be provided with a priming dot.

According to a further aspect of the invention, a tape system for a dose counter for an inhaler has a main elongate tape structure, and dosing indicia and tape positioning indicia located on the tape structure. The tape positioning indicia may comprise at least one line extending across the tape structure. The tape system may comprise pixelated indicia located on the tape structure and spaced from the positioning indicia. The tape system may comprise a priming dot located on the tape structure. The positioning indicia may be located between the timing dot and the pixelated indicia. The main elongate tape structure may have at least one end thereof wound on a bobbin or shaft.

A further aspect of the invention provides a method of designing an incremental dose counter for an inhaler comprising the steps of calculating nominal canister fire and dose counter positions for a dose counter actuator of the inhaler; calculating a failure/success rate for dose counters built to tolerance levels for counting each fire of inhalers in which the dose counter actuators may be applied; and selecting a tolerance level to result in said failure/success rate to be at or below/above a predetermined value. This is highly advantageous in that it allows an efficient and accurate prediction of the reliability of a series of inhaler counters made in accordance with the design.

The method of designing may include selecting the failure/success rate as a failure rate of no more than one in 50 million. The method of designing may include setting an average count position for dose counters built to the tolerances to be at or after an average fire position thereof during canister firing motion. The method of designing may include setting the average count position to be about 0.4 to 0.6 mm after the average fire position, such as about 0.48 mm after. The method of designing may include setting tolerances for the standard deviation of the fire position in dose counters built to the tolerances to be about 0.12 to 0.16 mm, such as about 0.141 mm. The method of designing may include setting tolerances for the standard deviation of the count positions in dose counters built to the tolerances to be about 0.07 to 0.09 mm, such as about 0.08 mm. A further aspect of the invention provides a computer implemented method of designing an incremental dose counter for an inhaler which includes the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing in a production run a series of incremental dose counters for inhalers which comprises manufacturing the series of dose counters in accordance with the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing a series of incremental dose counters for inhalers, which comprises manufacturing the dose counters with nominal canister fire and dose count positions of a dose counter actuator relative to a dose counter chassis (or inhaler main body), and which includes building the dose counters with the average dose count position in the series being, in canister fire process, at or after the average canister fire position in the series.

According to a further aspect of the invention, the method provides fitting each dose counter in the series of incremental dose counters to a corresponding main body of an inhaler.

These aspects advantageously provide for the production run of a series of inhalers and dose counters which count reliably in operation.

According to a further aspect of the invention, an incremental dose counter for a metered dose inhaler has a body arranged to retain a canister for movement of the canister relative thereto, the incremental dose counter having a main body, an actuator arranged to be driven and to drive an incremental output member in a count direction in response to canister motion, the actuator being configured to restrict motion of the output member in a direction opposite to the count direction. This advantageously enables an inhaler dose counter to keep a reliable count of remaining doses even if dropped or otherwise jolted.

The output member may comprise a ratchet wheel. The actuator may comprise a pawl and in which the ratchet wheel and pawl are arranged to permit only one-way ratcheting motion of the wheel relative to the pawl. The dose counter may include an anti-back drive member fixed to the main body. In a rest position of the dose counter, the ratchet wheel is capable of adopting a configuration in which a back surface of one tooth thereof engages the anti-back drive member and the pawl is spaced from an adjacent back

surface of another tooth of the ratchet wheel without positive drive/blocking engagement between the pawl and wheel.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention may be carried out in various ways and preferred embodiment of a dose counter, inhaler and methods of assembly, design and manufacture will now be described with reference to the accompanying drawings in which:

FIG. **1** is an isometric view of a main body of an embodiment of an inhaler related to the invention together with a mouthpiece cap therefor;

FIG. **2** is a top plan view of the components as shown in FIG. **1**;

FIG. **3**A is a section on the plane **3**A-**3**A in FIG. **2**;

FIG. **3**B is a view corresponding to FIG. **3**A but with a dose counter fitted to the main body of the inhaler;

FIG. **4**A is an exploded view of the inhaler main body, mouthpiece cap, dose counter and a dose counter window;

FIG. **4**B is a view in the direction **4**B in FIG. **4**C of a spring retainer of the dose counter;

FIG. **4**C is a top view of the spring retainer of FIG. **4**B;

FIG. **5** is a bottom view of the assembled inhaler main body, mouthpiece cap, dose counter and dose counter window;

FIGS. **6**A, **6**B, **6**C, **6**D, **6**E, **6**F, **6**G and **6**H are various views of dose counter components of the inhaler;

FIGS. **7**A and **7**B are sectional views showing canister clearance inside the main body of the inhaler;

FIG. **7**C is a further sectional view similar to that of FIG. **7**B but with the canister removed;

FIG. **7**D is a top plan view of the inhaler main body;

FIGS. **8**A, **8**B, **8**C and **8**D show the inhaler main body and dose counter components during assembly thereof;

FIG. **9** shows a sectional side view of a datum line for an actuator pawl of the dose counter;

FIGS. **10**A, **10**B, **10**C, **10**D, **10**E and **10**F show various side views of positions and configurations of the actuator pawl, a ratchet wheel, and a count pawl;

FIG. **11** shows distributions for tolerances of start, reset, fire, count and end positions for the actuator of the dose counter;

FIG. **12** is an enlarged version of part of FIG. **4**A;

FIG. **13** shows an end portion of a tape of the dose counter;

FIG. **14** shows a computer system for designing the dose counter;

FIG. **15** is an isometric view of a stock bobbin modified in accordance with the present invention for use in the dose counter of the inhaler of FIGS. **1** to **14**;

FIG. **16** shows an end view of the stock bobbin of FIG. **15**;

FIG. **17** is a section through a longitudinal axis of the stock bobbin of FIGS. **15** and **16**;

FIGS. **18**A, **18**B and **18**C are views of the stock bobbin of FIGS. **15** to **17** mounted in the dose counter chassis of FIGS. **1** to **14**, with the control elements of the forks of the second shaft (or split pin) having a profile slightly different to that in FIG. **6**F, with the forks in a compressed configuration;

FIGS. **19**A, **19**B and **19**C are views equivalent to FIGS. **18**A to **18**C but with the forks in a more expanded configuration due to a different rotational position of the stock bobbin;

FIG. **20** is an isometric view of the chassis assembled and including the stock bobbin of FIGS. **15** to **17** but excluding the tape for reasons of clarity;

FIG. **21** is a view of a preferred embodiment of a dry powder inhaler in accordance with the present invention;

FIG. **22** is an exploded view of the inhaler of FIG. **21**;

FIG. **23** is a view of a dose counter of the inhaler of FIG. **21**;

FIG. **24** is an exploded view of the dose counter shown in FIG. **23**;

FIG. **25** is an exploded view of parts of the inhaler of FIG. **21**; and

FIG. **26** is a view of a yoke of the inhaler of FIG. **21**.

DETAILED DESCRIPTION OF THE INVENTION

FIG. **1** shows a main body **10** of a manually operated metered dose inhaler **12** in accordance with an embodiment related to the present invention and having a mouthpiece cap **14** securable over a mouthpiece **16** of the main body.

The main body has a canister chamber **18** into which a canister **20** (FIG. **7**A) is slideable. The canister **20** has a generally cylindrical main side wall **24**, joined by a tapered section **26** to a head portion **28** having a substantially flat lower face **30** which has an outer annular drive surface **32** arranged to engage upon and drive an actuation pin **34** of a dose counter **36** as will be described. Extending centrally and axially from the lower face **30** is a valve stem **38** which is arranged to sealingly engage in a valve stem block **40** of the main body **10** of the inhaler **12**. The valve stem block **40** has a passageway **42** leading to a nozzle **44** for directing the contents of the canister **20**, namely active drug and propellant, towards an air outlet **46** of the inhaler main body **12**. It will be appreciated that due to gaps **48** between the canister **20** and an inner wall **50** of the main body **10** of the inhaler **12** an open top **52** of the main body **10** forms an air inlet into the inhaler **12** communicating via air passageway **54** with the air outlet **46**, such that canister contents exiting nozzle **44** mix with air being sucked by the user through the air passageway **54** in order to pass together through the air outlet and into the mouth of the user (not shown).

The dose counter **36** will now be described. The dose counter **36** includes an actuation pin **34** biased upwardly from underneath by a return spring **56** once installed in the main body **10**. As best shown in FIGS. **4**A, **6**H and **8**A, the pin **34** has side surfaces **58**, **60** arranged to slide between corresponding guide surfaces **62**, **64** located in a dose counter chamber **66** of the main body **10**, as well as an end stop surface **68** arranged to engage a corresponding end stop **70** formed in the dose counter chamber **66** to limit upward movement of the pin **34**. The pin **34** has a top part **72** which is circularly cylindrical and extends through an aperture **74** formed through a separator wall **76** which separates the canister chamber **18** from the dose counter chamber **66**. The top part **72** of the pin **34** has a flat top surface **78** which is arranged to engage the outer annular drive surface **32** of the canister **20**.

The actuation pin **34** is integrally formed with a drive or actuator pawl **80**. The actuator pawl **80** has a generally inverted U-shape configuration, having two mutually spaced and parallel arms **82**, **84** extending from a base portion of the actuation pin **34**, each holding at respective distal ends **88** thereof opposite ends of a pawl tooth member **90** which extends in a direction substantially perpendicular to the arms **82**, **84**, so as to provide what may be considered a "saddle" drive for pulling on each of the 11 drive teeth **92** of a ratchet wheel **94** of an incremental drive system **96** or ratchet mechanism **96** of the dose counter **36**. As shown for example in FIG. **10**B, the pawl tooth member **90** has a sharp lower

longitudinal side edge **98** arranged to engage the drive teeth **92**, the edge-to-surface contact provided by this engagement providing very accurate positioning of the actuator pawl **80** and resultant rotational positioning of the ratchet wheel **94**.

The dose counter **36** also has a chassis preassembly **100** which, as shown in FIGS. **4**A and **6**A, includes a chassis **102** having a first shaft **104** receiving the ratchet wheel **94** which is secured to a tape reel shaft **106**, and a second shaft (or split pin) **108** which is parallel to and spaced from the first shaft **104** and which slidably and rotationally receives a tape stock bobbin **110**.

As shown in FIG. **6**B, when the inhaler has not been used at all, the majority of a tape **112** is wound on the tape stock bobbin **110** and the tape **112** has a series of regularly spaced numbers **114** displayed therealong to indicate a number of remaining doses in the canister **20**. As the inhaler is repeatedly used, the ratchet wheel **94** is rotated by the actuator pawl **80** due to operation of the actuation pin **34** by the canister **20** and the tape **112** is incrementally and gradually wound on to the tape reel shaft **106** from the second shaft **108**. The tape **112** passes around a tape guide **116** of the chassis **102** enabling the numbers **114** to be displayed via a window **118** in a dose counter chamber cover **120** having a dose marker **132** formed or otherwise located thereon.

As shown in FIGS. **6**A and **6**D, the second shaft **108** is forked with two forks **124**, **126**. The forks **124**, **126** are biased away from one another. The forks have located thereon at diametrically opposed positions on the second shaft **108** friction or control elements **128**, **130**, one on each fork. Each control element extends longitudinally along its respective fork **124**, **126** and has a longitudinally extending friction surface **132**, **134** which extends substantially parallel to a longitudinal axis of the second shaft and is adapted to engage inside a substantially cylindrical bore **136** inside the tape stock bobbin **110**. This control arrangement provided between the bore **136** and the control elements **128**, **130** provides good rotational control for the tape stock bobbin **110** such that it does not unwind undesirably such as when the inhaler is dropped. The tape force required to unwind the tape stock bobbin **110** and overcome this friction force is approximately 0.1 N.

As can be seen in FIG. **6**D, as well as FIGS. **6**G and **10**A to **10**F, the chassis **102** is provided with an anti-back drive tooth **138** or count pawl **138** which is resiliently and substantially fixedly mounted thereto. As will be described below and as can be seen in FIGS. **10**A to **10**F, when the actuation pin **34** is depressed fully so as to fire the metered valve (not shown) inside the canister **20**, the actuator pawl **80** pulls down on one of the teeth **92** of the ratchet wheel **94** and rotates the wheel **94** anticlockwise as shown in FIG. **6**D so as to jump one tooth **92** past the count pawl **138**, thereby winding the tape **112** a distance incrementally relative to the dose marker **122** on the dose counter chamber **120** so as to indicate that one dose has been used.

With reference to FIG. **10**B, the teeth of the ratchet wheel **94** have tips **143** which are radiused with a 0.1 mm radius between the flat surfaces **140**, **142**. The ratchet wheel **94** has a central axis **145** which is 0.11 mm above datum plane **220** (FIG. **9**). A top/nose surface **147** of the anti-back drive tooth **138** is located 0.36 mm above the datum plane **220**. The distance vertically (i.e. transverse to datum plane **220**—FIG. **9**) between the top nose surface **147** of the anti-back drive tooth is 0.25 mm from the central axis **145** of the wheel **94**. Bump surface **144** has a lateral extent of 0.20 mm, with a vertical length of a flat **145'** thereof being 1 mm, the width of the bump surface being 1.22 mm (in the direction of the axis **145**), the top **149** of the bump surface **144** being 3.02 mm vertically below the axis **145**, and the flat **145'** being spaced a distance sideways (i.e. parallel to the datum plane **220**) 2.48 mm from the axis **145**. The top surface **78** of the pin **34** (FIG. **6**H) is 11.20 mm above the datum plane **220** (FIG. **9**) when the actuator pawl **80** and pin **34** are in the start configuration. The length of the valve stem **22** is 11.39 mm and the drive surface **32** of the canister **20** is 11.39 mm above the datum plane **220** when the canister is at rest waiting to be actuated, such that there is a clearance of 0.19 mm between the canister **20** and the pin **34** in this configuration.

FIGS. **10**A and **10**B show the actuator pawl **80** and ratchet wheel **94** and count pawl **138** in a start position in which the flat top **78** of the pin **34** has not yet been engaged by the outer annular drive surface **32** of the canister **20** or at least has not been pushed down during a canister depression.

In this "start" position, the count pawl **138** engages on a non-return back surface **140** of one of the teeth **92** of the ratchet wheel **94**. The lower side edge **98** of the actuator pawl is a distance "D" (FIG. **9**) 1.33 mm above datum plane **220** which passes through bottom surface or shoulder **41** of valve stem block **40**, the datum plane **220** being perpendicular to a main axis "X" of the main body **10** of the inhaler **12** which is coaxial with the centre of the valve stem block bore **43** and parallel to a direction of sliding of the canister **20** in the main body **10** of the inhaler **12** when the canister is fired.

As shown in FIG. **10**B, an advantageous feature of the construction is that the pawl tooth/actuator **90** acts as a supplementary anti-back drive member when the inhaler **12** is not being used for inhalation. In particular, if the inhaler **12** is accidentally dropped, resulting in a jolt to the dose counter **36** then, if the wheel **94** would try to rotate clockwise (backwards) as shown in FIG. **10**B, the back surface **140** of a tooth will engage and be blocked by the tooth member **90** of the pawl **80**. Therefore, even if the anti-back drive tooth **138** is temporarily bent or overcome by such a jolt, undesirable backwards rotation of the wheel **94** is prevented and, upon the next canister firing sequence, the pawl **90** will force the wheel **94** to catch up to its correct position so that the dose counter **36** continues to provide correct dosage indication.

FIG. **10**C shows a configuration in which the actuator pawl **80** has been depressed with the pin **34** by the canister **20** to a position in which the side edge **98** of the pawl tooth member **90** is just engaged with one of the teeth **92** and will therefore upon any further depression of the pin **34** begin to rotate the wheel **94**. This is referred to as a "Reset" position or configuration. In this configuration, the lower side edge **98** of the actuator **80** is 0.64 mm above the datum plane **220**.

FIG. **10**D shows a configuration in which the actuator pawl **80** has been moved to a position lower than that shown in FIG. **10**C and in which the metered dose valve (not shown) inside the canister has at this very position fired in order to eject active drug and propellant through the nozzle **44**. It will be noted that in this configuration the count pawl **138** is very slightly spaced from the back surface **140** of the same tooth **92** that it was engaging in the configuration of FIG. **10**D. The configuration shown in FIG. **10**D is known as a "Fire" configuration. In this configuration the lower side edge **98** of the actuator **80** is 0.47 mm below the datum plane **220**.

FIG. **10**E shows a further step in the sequence, called a "Count" position in which the actuator pawl **80** has rotated the ratchet wheel **94** by the distance circumferentially angularly between two of the teeth **92**, such that the count pawl **138** has just finished riding along a forward surface **142** of one of the teeth **92** and has resiliently jumped over the tooth

into engagement with the back surface **140** of the next tooth. Accordingly, in this "Count" configuration, a sufficiently long stroke movement of the pin **34** has occurred that the tape **112** of the dose counter **36** will just have counted down one dose. In this configuration, the lower side edge **98** of the actuator is 0.95 mm below the datum plane **220**. Accordingly, in this position, the actuator **80** generally, including edge **98**, is 0.48 mm lower than in the fire configuration. It has been found that, although the count configuration happens further on than the fire configuration, counting is highly reliable, with less than 50 failed counts per million. This is at least partially due to momentum effects and to the canister releasing some back pressure on the user in some embodiments as its internal metering valve fires.

In the configuration of FIG. **10**F, the pawl **80** has been further depressed with the pin **34** by the canister **20** to a position in which it is just disengaging from one of the teeth **92** and the actuator pawl **80** is assisted in this disengagement by engagement of one of the arms **84** with a bump surface **144** on the chassis **102** (see FIG. **6**G) and it will be seen at this point of disengagement, which is called an "End" configuration, the count pawl **138** is positioned exactly halfway or substantially halfway between two of the drive teeth **92**. This advantageously means therefore that there is a minimum chance of any double counting or non-counting, which would be undesirable. In the end configuration, the side edge **98** of the actuator is 1.65 mm below the datum plane **220**. It will be appreciated that any further depression of the actuator pawl **80** and pin **34** past the "End" configuration shown in FIG. **10**F will have no effect on the position of the tape **112** displayed by the dose counter **36** since the actuator pawl **80** is disengaged from the ratchet wheel **94** when it is below the position shown in FIG. **10**F.

As shown in FIGS. **7**C and **7**D, the inner wall **50** of the main body **10** is provided with a two-step support rail **144** which extends longitudinally along inside the main body and is located directly adjacent the aperture **74**. As shown in FIG. **7**B a diametrically opposed two-step support rail **146** is also provided and this diametrically opposed in the sense that a vertical plane (not shown) can pass substantially directly through the first rail **144**, the aperture **74**, a central aperture **148** of the valve stem block **40** (in which canister stem **25** is located) and the second two-step support rail **146**. As shown in FIG. **7**A and schematically in FIG. **7**B, the rails **144**, **146** provide a maximum clearance between the canister **20** and the rails **144**, **146** in a radial direction of almost exactly 0.3 mm, about 0.25 to 0.35 mm being a typical range. This clearance in this plane means that the canister **20** can only rock backwards and forwards in this plane towards away from the actuation pin **34**. A relatively small distance and this therefore prevents the canister wobbling and changing the height of the actuation pin **34** a as to undesirably alter the accuracy of the dose counter **36**. This is therefore highly advantageous.

The inner wall **50** of the main body **10** is provided with two further two-step rails **150** as well as two pairs **152**, **154** of rails extending different constant radial amounts inwardly from the inner wall **50**, so as to generally achieve a maximum clearance of almost exactly 0.3 mm around the canister **20** for all of the rails **144**, **146**, **150**, **152**, **154** spaced around the periphery of the inner wall **50**, in order to prevent undue rocking while still allowing canister motion freely inside the inhaler **12**. It will be clear from FIG. **7**C for example that the two-step rails have a first portion near an outlet end **156** of the canister chamber **18**, the first portion having a substantially constant radial or inwardly-extending width, a first step **160** leading to a second portion **162** of the rail, the second portion **102** having a lesser radial or inwardly extending extent than the first portion **156**, and finally a second step **164** at which the rail merges into the main inner wall **50** main surface.

A method of assembling the inhaler **12** will now be described.

With reference to FIG. **8**A, the main body **10** of the inhaler **12** is formed by two or more plastics mouldings which have been joined together to the configuration shown.

As shown in FIG. **8**B, the actuator pawl **80** and pin **34** are translated forward into position into a pin receiving area **166** in the dose counter chamber **66** and the pin **34** and actuator **80** may then be raised until the pin **34** emerges through the aperture **74**.

Next, the return spring **56** may be inserted below the pin **34** and a generally cylindrical annular lower end **168** of the spring **56** may be moved by a tweezer or tweezer-like assembly tool (not shown) into engagement with a shelf **170** of a spring retainer **172** in the dose counter chamber **66**. The spring retainer **172** is U-shaped and the shelf **170** is U-shaped and has a recess **174** formed below it. As shown in FIGS. **4**B, **4**C and **12** shelf **170** includes three chamfer surfaces **176**, **178**, **180** arranged to assist in moving the lower end of the spring **168** into position onto the shelf using the assembly tool (not shown). Once the lower end of the spring **168** is in place, the assembly tool (not shown) can easily be removed at least partly via the recess **174** below the lower end **168** of the spring **56**.

The tape **112** is attached at one end (not shown) to the tape stock bobbin **110** and is wound onto the bobbin by a motor **200** (FIG. **13**) having a hexagonal output shaft **202** which engages in a hexagonal socket **204** (FIG. **6**B) of the bobbin. During winding, the tape is monitored by a sensor **206**, which may be in the form of a camera or laser scanner, which feeds data to a computer controller **205** for the motor **200**. The controller **205** recognises three positioning markers **210** in the form of lines across the tape **112** and stops the motor **202** when the tape **112** is nearly fully wound onto the bobbin **110**, such that the distal end **212** of the tape **112** can be secured, e.g. by adhesive, to the tape reel shaft **106**. The controller **205** also recognises a pixelated tape size marker **214** observed by the sensor **206** and logs in a stocking system data store **217** details of the tape **112** such as the number of numbers **114** on the tape, such as one hundred and twenty or two hundred numbers **114**. Next, the tape reel shaft is wound until an appropriate position of the lines **210** at which a priming dot **216** will, once the bobbin **110** and reel shaft **106** are slid onto the second shaft **108** and second shaft **104**, be in a position to be located in the window **118** when the inhaler **12** is fully assembled. In the embodiments, the bobbin **110** and reel shaft **106** may be slid onto the shafts **108**, **104** before the tape **112** is secured to the reel shaft **106** and the reel shaft may then be wound to position the priming dot **216**.

Next, the assembled dose counter components of the chassis preassembly **100** shown in FIG. **6**B may as shown in FIG. **8**C be inserted into the dose counter chamber **66**, with pins **182**, **184**, **186** formed on the main body **10** in the dose counter chamber **66** passing through apertures or slots **188**, **190**, **192** formed on the chassis **102**, such that the pins **182**, **184**, **186** extend through (or at least into) the apertures or slots **188**, **190**, **192**. With the chassis **102** being relatively firmly pushed towards the main body **10**, the pins **182**, **184**, **186** are then heat staked and the chassis **102** is therefore after this held very firmly in position in the main body and is unable to move, thereby assisting in providing great accuracy for the dose counter **36**. Next, as shown in FIG. **8**D, the

dose counter chamber cover **120** may be fitted over the dose counter chamber **66** and may be secured in place such as by welding, with the priming dot **216** being displayed through the window.

The user can, when readying the inhaler **12** for first use, prime the inhaler by depressing the canister **20** three times which will bring the first number **114** on the tape into display through the window **118** in place of the priming dot **216**, the number **114** shown in FIG. **8**D being "200", thereby indicating that 200 doses are remaining to be dispensed from the canister **20** and inhaler **12**.

As shown in FIG. **8**D, and in FIG. **5**, an open drain hole **194** is provided at the bottom of the dose counter chamber **66** by a substantially semi-circular cut-out or recess formation **196** in a lower surface **198** of the main body **10** of the inhaler. Accordingly, if the user (not shown) should decide to wash the main body **10** of the inhaler, for example after encountering an unhygienic situation or simply as a matter of choice, the drain hole **194** allows initial draining of water from inside the dose counter chamber **66** and also thereafter evaporation of water or any aqueous matter in the dose counter chamber **66** so that the window **118** does not mist up undesirably.

FIG. **14** shows a computer system **230** for designing the dose counter **36** and in particular for calculating distributions representative of average positions and standard deviations in a production series of inhalers of the start, reset, fire, count and end positions of the actuator lower side edge **98** relative to the datum plane **220** (FIG. **9**) and therefore of the actuator pawl **80** generally relative to the ratchet wheel **94**, chassis **102** and, when the inhaler **12** is fully assembled, the main body **10** of the inhaler **12**. The computer system **230** includes a data store **232**, a CPU **234**, an input device **236** (such as a keyboard or communication port) and an output device **238** (such as a communications port, display screen and/or printer). A user may enter data via the input device **236** which may be used by the CPU **234** in a mathematical calculation to predict count failure rates when the various dose counters are to be built in a series with dose counter positions set with given averages and standard deviations and taking into account any momentum/inertia effects and metering valve user-back-pressure reduction effect which will occur upon canister firing of a given type of canister. The computer system **230** is thus mathematically used to design the distributions. For the inhaler **12** described herein with the dose counter **36** and canister **20**, the distributions are designed as shown in FIG. **11**. The x axis shows distance of the lower side surface **98** of the actuator **80** above the datum plane **220** and the y axis is representative of the distribution. Thus, curve **240** shows that the start configuration has an average 1.33 mm above the datum plane **200** (standard deviation is 0.1 mm), curve **242** shows that the reset configuration has an average of 0.64 mm above the datum plane **220** (standard deviation is 0.082 mm), curve **244** shows the fire configuration has an average 0.47 mm below the datum plane **220** (standard deviation is 0.141 mm), curve **246** shows the count configuration has an average 0.95 mm below the datum plane **220** (standard deviation is 0.080 mm), and curve **248** shows the end configuration has an average of 1.65 mm below the datum plane **220** (standard deviation is 0.144 mm).

FIGS. **15** to **20** show a version of the inhaler modified in accordance with the present invention. In these drawings, the same reference numerals have been used to those in the earlier drawings to denote the equivalent components. The inhaler **12** is the same as that in FIGS. **1** to **14** apart from the following modifications.

First, it can be seen that there is a modification in that the drive teeth **92** of the ratchet wheel **94** have a different profile to that in FIGS. **1** to **14**. There are also only nine ratchet teeth **94** in this embodiment instead of eleven.

Additionally, as shown in FIGS. **18**C and **19**C, the control elements **128**, **130** on the forks **124**, **126** of the second shaft **108** have a tapered profile which is different to the profile of the control elements **128**, **130** shown in FIG. **6**F. Either profile can be used in the embodiment of FIGS. **15** to **20** however.

Furthermore, as shown in FIG. **15**, the tape stock bobbin **110** has an inwardly facing generally cylindrical engagement surface **300** with a wavelike form extending partially therealong. The engagement surface **300** has a cross-section **301** perpendicular to the longitudinal length of the stock bobbin **110** which is constant therealong. This cross-section **301** can be seen in FIG. **16** and consists of a series of ten regularly spaced concavities **302** and ten convex wall portions **304**. The convex wall portions **304** are equi-spaced between the concavities **302**. Each concavity **302** has a radius of 0.2 mm. Each convex wall portion **304** also has a radius of 0.2 mm. Finally, the cross section **301** also includes flat wall portions **306** between all of the radiused wall portions of the concavities **302** and convex wall portions **304**. The geometry of the cross-section **301** is therefore defined by the radii of the concavities **302** and convex wall portions **304**, the flat wall portions **306** and the fact that there are ten concavities **302** and convex wall portions **304**.

The minor diameter of the engagement surface **300**, i.e. between the tips of opposite convex wall portions **304**, is 2.46 mm. The major diameter of the engagement surface **300**, i.e. between the outermost portions of the concavities **302**, is 2.70 mm. The undeformed tip to tip maximum diameter of the forks **124**, **126** of the split pin (the second shaft) **108**, i.e. in the region of the maximum radio extent of the control elements **128**, **130**, is 3.1 millimeters and it will therefore be appreciated that the forks **124**, **126** are resiliently compressed once the stock bobbin **110** has been assembled onto the split pin **108** in all rotational configurations of the stock bobbin **110** relative to the split pin **108**. The minimum gap between the forks **124**, **126** in the plane of the cross sections of FIGS. **18**C and **19**C is 1 mm when the split pin **108** is in the undeformed, pre-inserted state. When the split pin **108** is at maximum compression, as shown in FIGS. **18**A to **18**C when the control elements **128**, **130** are shown to be engaged on top of the convex wall portions **304**, the gap **308** between the tips **310**, **312** of the forks **124**, **126** is 0.36 mm. On the other hand, when the split pin **108** is at minimum compression (once inserted into the stock bobbin) as shown in FIGS. **19**A to **19**C, when the control elements **128**, **130** rest in the concavities **302**, the gap between the tips **310**, **312** of the forks **124**, **126** is 0.6 mm. The control elements **128**, **130** are outwardly radiused with a radius also of 0.2 mm such that they can just rest on the concavities **302** with full surface contact (at least at an axial location on the split pin where the tapered control elements are at their maximum radial extent), without rattling in, locking onto or failing to fit in the concavities **302**. The radii of the control elements **128**, **130** is therefore preferably substantially the same as the radii of the concavities **302**

It will be appreciated that whereas FIGS. **18**B and **19**B are end views along the coaxial axis of the stock bobbin **110** and split pin **108**, FIGS. **18**A and **19**A are cross-sections. FIG. **19**A is a section on the plane A-A' in FIG. **19**C and FIG. **18**A is a section at the same plane, but of course with the stock bobbin **110** rotated relative to the split pin **108**.

As the inhaler **12** is used and the ratchet wheel **94** rotates in order to count used doses, the stock bobbin rotates incrementally through rotational positions in which rotation is resisted, i.e. due to increasing compression of the split pin **108** at such rotational positions, and rotational positions in which rotation is promoted, i.e. due to decreasing compression of the split pin **108** at such rotational positions and this may involve a click forward of the stock bobbin **110** to the next position equivalent to that in FIGS. **19**A to **19**C in which the control elements **128**, **130** of the split pin art located in the concavities **302**. This functionality firstly allows the stock bobbin to unwind during use as required, but also prevents the tape **112** from loosening during transit if the inhaler **12** is dropped, such as onto a hard surface. This is highly advantageous, since the tape **11** is prevented from moving to a position in which it will give an incorrect reading regarding the number of doses in the canister.

During compression and expansion of the forks in the radial direction between the two configurations shown in FIGS. **18**C and **19**C, the forks **124**, **126** rotate about a point **316** on the split pin where the forks **124**, **126** come together. This rotational action means that there is a camming action between the forks **124**, **126** and the engagement surface **300** without significant friction but, nevertheless, the resilient forces provided by the regulator formed by the engagement surface **300** and forks **124**, **126** are able to regulate unwinding of the tape such that it does not easily occur during transit or if the inhaler **12** is dropped. It has been found during testing that a force of 0.3 to 0.4 N needs to be applied to the tape **112** to overcome the regulator at the stock bobbin **110**. 0.32 N is achieved with the control elements **128** having the profile shown in FIG. **19**C and 0.38 N is achieved with the profile of the control elements **128** altered to be as shown as described with reference to FIG. **6**F. These forces are substantially higher than the 0.1 N force mentioned above and undesirable movement of the tape is substantially avoided even if the inhaler is dropped onto a hard surface. The modified arrangement of FIGS. **15** to **20** does not provide this force "constantly" such that there is overall not an undesirably high friction of the tape **112** as it passes over the other components of the dose counter because, due to the incremental nature of the resilient forces at the regulator, the tape **112** can incrementally relax as it slides over the stationary chassis components.

Instead of having ten concavities **302** and convex wall portions **304**, other numbers may be used, such as 8 or 12. However, it is preferred to have an even number, especially since two control elements **128**, **130** are provided, so that all of the control elements **128**, **130** will expand and contract simultaneously. However, other arrangements are envisaged with 3 or more forks and the number of concavities/convex wall portions may be maintained as an integer divisible by the number of forks to maintain a system with simultaneous expansion/contraction. For example, the use of 9, 12 or 15 concavities/convex wall portions with 3 forks is envisaged.

Instead of having the engagement surface **300** on the inside of the stock bobbin **110**, it could be placed on the outside of the stock bobbin **110** so as to be engaged by flexible external legs/pawls or similar.

It will be noted that the regulator provided by the engagement surface **300** and forks **124**, **126** does not only allow rotation of the stock bobbin in one direction as is the case with the ratchet wheel **94**. Rotation in both directions is possible, i.e. forwards and backwards. This means that during assembly, the stock bobbin **110** can be wound backwards during or after fitting the bobbin **100**, shaft **106** and tape **112** onto the carriage **102**, if desired.

The stock bobbin **110** and the carriage **102** including the split pin **108** are both moulded of polypropylene material.

It will be seen from FIG. **16** that the cross-sectional shape **301** is not symmetrical within the hexagonal socket **204**. This has enabled the hexagonal socket **204** to be maintained at a useful size while still allowing the desired size and geometry of the cross section **301** to fit without interfering with the hexagonal shape of the hexagonal socket **204** and also permits moulding to work during manufacture.

As shown in FIG. **17**, the stock bobbin **110** has a series of four circumferential ribs **330** inside it and a spaced therealong. These hold the stock bobbin **110** on the correct side of the mould tool during moulding.

FIGS. **21** and **22** show a preferred embodiment in accordance with the invention of an inhaler **510** for dispensing a dry-powdered medicament in metered doses for patient inhalation. The inhaler **510** is as disclosed in FIGS. **1** to **16** or EP-A-1330280, the contents of which are hereby fully incorporated herein by reference, but with the stock bobbin **110** and second shaft **108** of the dose counter **516** modified so as to be as in FIGS. **15** to **20** hereof. Thus, the dry powder inhaler **510** generally includes a housing **518**, and an assembly **512** received in the housing (see FIG. **21**). The housing **518** includes a case **520** having an open end **522** and a mouthpiece **524** (FIG. **25**) for patient inhalation, a cap **526** secured to and closing the open end **522** of the case **520**, and a cover **528** pivotally mounted to the case **520** for covering the mouthpiece **524**. As shown in FIG. **22**, the inhaler **510** also includes an actuation spring **569**, first yoke **566** with opening **572**, bellows **540** with crown **574**, a reservoir **514**, second yoke **568** with hopper **542** and dose counter **516** mounted thereto, and case **520** has transparent window **5130** thereon for viewing dose counter tape indicia **5128**. The dose metering system also includes two cams **570** mounted on the mouthpiece cover **528** and movable with the cover **528** between open and closed positions. The cams **570** each include an opening **580** for allowing outwardly extending hinges **582** of the case **520** to pass therethrough and be received in first recesses **584** of the cover **528**. The cams **570** also include bosses **586** extending outwardly and received in second recesses **588** of the cover **528**, such that the cover **528** pivots about the hinges **582** and the cams **570** move with the cover **528** about the hinges **582**. As described in EP-A-1330280, cams **570** act upon cam followers **578** to move second yoke **568** up and down and thereby operate dose counter by engagement of pawl **5138** on the second yoke **568** with teeth **5136**. Remaining components of the inhaler are provided as, and operate as described, in EP-A-1330280.

The dose counting system **516** therefore includes a ribbon or tape **5128** (FIGS. **23** & **24**), having successive numbers or other suitable indicia printed thereon, in alignment with a transparent window **5130** provided in the housing **18** (see FIG. **22**). The dose counting system **516** includes the rotatable stock bobbin **110** (as described above), an indexing spool **5134** rotatable in a single direction, and the ribbon **5128** rolled and received on the bobbin **110** and having a first end **5127** secured to the spool **5134**, wherein the ribbon **5128** unrolls from the bobbin **110** so that the indicia are successively displayed as the spool **5134** is rotated or advanced. In FIGS. **23** and **24** the wavelike engagement surface **300** of the bobbin **110** is not shown for the purposes of clarity.

The spool **134** is arranged to rotate upon movement of the yokes **566**, **568** to effect delivery of a dose of medicament from reservoir **514**, such that the number on the ribbon **5128** is advanced to indicate that another dose has been dispensed by the inhaler **510**. The ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase or

decrease upon rotation of the spool **5134**. For example, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, decrease upon rotation of the spool **5134** to indicate the number of doses remaining in the inhaler **510**. Alternatively, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase upon rotation of the spool **5134** to indicate the number of doses dispensed by the inhaler **10**.

The indexing spool **5134** includes radially extending teeth **5136**, which are engaged by pawl **5138** extending from a cam follower **578** of the second yoke **568** upon movement of the yoke to rotate, or advance, the indexing spool **5134**. More particularly, the pawl **5138** is shaped and arranged such that it engages the teeth **5136** and advances the indexing spool **5134** only upon the mouthpiece cover **528** being closed and the yokes **566**, **568** moved back towards the cap **526** of the housing **518**.

The dose counting system **516** also includes a chassis **5140** that secures the dose counting system to the hopper **542** and includes shafts **108**, **5144** for receiving the bobbin **110** and the indexing spool **5134**. As described above with reference to FIGS. **1** to **20**, the bobbin shaft **108** is forked and includes radially nubs **5146** for creating a resilient resistance to rotation of the bobbin **110** on the shaft **108** by engaging with the wavelike engagement surface **300** inside the bobbin **110**. A clutch spring **5148** is received on the end of the indexing spool **5134** and locked to the chassis **5140** to allow rotation of the spool **5134** in only a single direction.

Various modifications may be made to the embodiment shown without departing from the scope of the invention as defined by the accompanying claims as interpreted under patent law.

What is claimed is:

1. An inhaler for metered dose inhalation, the inhaler comprising:

a main body having a canister housing,

a medicament canister, which is moveable relative to the canister housing and retained in a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister, and

a dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,

wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall,

wherein the canister housing has a longitudinal axis X which passes through the center of the central outlet port, and

wherein the first inner wall canister support formation, the actuation member, and the central outlet port lie in a common plane coincident with the longitudinal axis X such that the first inner wall canister support formation protects against unwanted actuation of the dose counter by reducing rocking of the medicament canister relative to the main body of the inhaler.

2. The inhaler as claimed in claim **1** wherein the medicament canister is movable relative to the dose counter.

3. The inhaler as claimed in claim **1** further comprising an aperture formed in the inner wall through which the portion of the actuation member extends.

4. The inhaler as claimed in claim **1**, wherein the first inner wall canister support formation comprises a support rail which extends longitudinally along an inside surface of the main body.

5. The inhaler as claimed in claim **4**, wherein the support rail includes a step formed thereon.

6. The inhaler as claimed in claim **4** further comprising a plurality of support rails each of which extends longitudinally along the inside surface of the main body.

7. The inhaler as claimed in claim **6**, wherein two of the plurality of support rails are positioned at opposite ends of the inside surface of the main body to face each other.

8. The inhaler as claimed in claim **4**, wherein the support rail includes two steps formed thereon, the steps being spaced apart longitudinally along an inside surface of the main body.

9. The inhaler as claimed in claim **4**, wherein the support rail merges with the inner wall at a location adjacent the aperture.

10. The inhaler as claimed in claim **9**, wherein a width dimension of the support rail is not constant, and the width dimension is greatest at the location where the support rail merges with the inner wall.

11. The inhaler as claimed in claim **1** further comprising a second inner wall canister support formation and wherein the second inner wall canister support formation, the first inner wall canister support formation, the actuation member and the central outlet port lie in a common plane coincident with longitudinal axis X.

12. An inhaler for metered dose inhalation, the inhaler comprising:

a main body having a canister housing,

a medicament canister, which is moveable relative to the canister housing and retained in a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister, and

a dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,

wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall,

wherein the canister housing has a longitudinal axis X which passes through the center of the central outlet port, and

wherein the first inner wall canister support formation, the actuation member, and the central outlet port lie in a common plane coincident with the longitudinal axis X such that the first inner wall canister support formation protects against dose count errors by reducing rocking of the medicament canister towards or away from the actuation member.

13. An inhaler for metered dose inhalation, the inhaler comprising:

a main body having a canister housing,

a medicament canister retained in the canister housing and movable relative thereto, and a dose counter, the dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,

wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall,

wherein the canister housing has an aperture formed in the inner wall through which the portion of the actuation member extends, and

wherein the first inner wall canister support formation extends from the main surface of the inner wall to the aperture.

14. The inhaler as claimed in claim **13** wherein the medicament canister is movable relative to the dose counter.

15. The inhaler as claimed in claim 13, wherein the first inner wall canister support formation comprises a support rail which extends longitudinally along an inside surface of the main body.

16. The inhaler as claimed in claim 15, wherein the support rail includes a step formed thereon.

17. The inhaler as claimed in claim 15 further comprising a plurality of support rails each of which extends longitudinally along the inside surface of the main body.

18. The inhaler as claimed in claim 17, wherein two of the plurality of support rails are positioned at opposite ends of the inside surface of the main body to face each other.

19. The inhaler as claimed in claim 15, wherein the support rail includes two steps formed thereon, the steps being spaced apart longitudinally along the inside surface of the main body.

20. The inhaler as claimed in claim 15, wherein a width dimension of the support rail is not constant, and the width dimension is greatest at the location where the support rail is closest to the aperture.

21. The inhaler as claimed in claim 13, wherein the first inner wall canister support formation, the aperture, and a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister, all lie in a common plane coincident with a longitudinal axis X which passes through the center of the central outlet port.

22. The inhaler as claimed in claim 21 further comprising a second inner wall canister support formation and wherein the second inner wall canister support formation, the first inner wall canister support formation, the aperture, and the central outlet port lie in a common plane coincident with longitudinal axis X.

* * * * *

EXHIBIT 3

8475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 9, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: *10,561,808*
ISSUE DATE: *February 18, 2020*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

John Burson
Certifying Officer

US010561808B2

(12) **United States Patent**
Walsh et al.

(10) **Patent No.: US 10,561,808 B2**
(45) **Date of Patent: Feb. 18, 2020**

(54) **DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR**

(71) Applicants: **IVAX PHARMACEUTICALS IRELAND**, Waterford (IE); **NORTON (WATERFORD) LIMITED**, Waterford (IE); **TEVA PHARMACEUTICALS IRELAND**, Waterford (IE)

(72) Inventors: **Declan Walsh**, County Kilkenny (IE); **Derek Fenlon**, County Wexford (IE); **Simon Kaar**, County Cork (IE); **Jan Geert Hazenberg**, County Kilkenny (IE); **Daniel Buck**, County Waterford (IE); **Paul Clancy**, Waterford (IE); **Robert Charles Uschold**, Leominster, MA (US); **Jeffrey A. Karg**, Hopkinton, MA (US)

(73) Assignees: **IVAX PHARMACEUTICALS IRELAND**, Waterford (IE); **NORTON (WATERFORD) LIMITED**, Waterford (IE); **TEVA PHARMACEUTICALS IRELAND**, Waterford (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 228 days.

(21) Appl. No.: **15/262,818**

(22) Filed: **Sep. 12, 2016**

(65) **Prior Publication Data**

US 2016/0375208 A1 Dec. 29, 2016

Related U.S. Application Data

(60) Continuation of application No. 14/699,584, filed on Apr. 29, 2015, which is a continuation of application
(Continued)

(51) **Int. Cl.**
A61M 15/00 (2006.01)
G06M 1/24 (2006.01)
A61M 11/00 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 15/0078*** (2014.02); ***A61M 11/00*** (2013.01); ***A61M 15/007*** (2014.02);
(Continued)

(58) **Field of Classification Search**
CPC A61M 15/0078; A61M 15/0025; A61M 15/0026; A61M 15/007; A61M 15/0071;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,174,890 A 11/1979 Johnson
4,669,838 A 6/1987 Hibbard
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2501726 9/2006
EP 1330280 7/2003
(Continued)

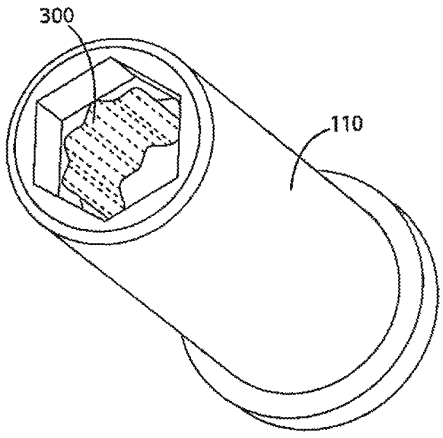
OTHER PUBLICATIONS

Final Office Action dated Oct. 20, 2016 for U.S. Appl. No. 14/699,567.
(Continued)

Primary Examiner — Daniel A Hess
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

A dose counter for an inhaler includes a counter display arranged to indicate dosage information, and a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input. A regulator is provided which is arranged
(Continued)



to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

29 Claims, 17 Drawing Sheets

Related U.S. Application Data

No. 14/103,353, filed on Dec. 11, 2013, now Pat. No. 9,526,850, which is a division of application No. 13/110,532, filed on May 8, 2011, now Pat. No. 8,978,966.

(60) Provisional application No. 61/345,763, filed on May 18, 2010, provisional application No. 61/417,659, filed on Nov. 29, 2010.

(52) **U.S. Cl.**
CPC ***A61M 15/009*** (2013.01); ***A61M 15/0025*** (2014.02); ***A61M 15/0026*** (2014.02); ***A61M 15/0065*** (2013.01); ***A61M 15/0071*** (2014.02); ***G06M 1/246*** (2013.01); *A61M 2202/064* (2013.01); *A61M 2205/6063* (2013.01); *A61M 2207/00* (2013.01); *A61M 2207/10* (2013.01); *Y10T 29/49* (2015.01); *Y10T 29/49764* (2015.01); *Y10T 29/49826* (2015.01)

(58) **Field of Classification Search**
CPC A61M 11/00; A61M 15/0065; A61M 15/009; G06M 1/246
USPC 235/8
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,687,359	A	8/1987	Barrus	
5,482,030	A	1/1996	Klein	
5,861,911	A	1/1999	Oosaka	
6,446,627	B1	9/2002	Bowman	
6,718,972	B2	4/2004	OLeary	
8,418,690	B2	4/2013	Power	
8,474,448	B2	7/2013	Oi	
8,978,966	B2	3/2015	Walsh et al.	
9,174,013	B2	11/2015	Walsh et al.	
9,463,289	B2	10/2016	Walsh et al.	
2002/0047021	A1	4/2002	Blacker	
2002/0078949	A1	6/2002	OLeary	
2002/0078950	A1*	6/2002	O'Leary	A61M 15/0045 128/200.22
2002/0084891	A1	7/2002	Mankins et al.	
2003/0209239	A1	11/2003	Rand	
2004/0089298	A1	5/2004	Haikarainen et al.	
2004/0095746	A1	5/2004	Murphy	
2005/0028815	A1	2/2005	Deaton	
2005/0087191	A1	4/2005	Morton	
2006/0096594	A1	5/2006	Bonney	
2006/0107949	A1	5/2006	Davies	
2006/0107979	A1	5/2006	Kim	
2007/0062518	A1	3/2007	Geser	
2008/0242465	A1	10/2008	Strobel	
2009/0178678	A1	7/2009	OLeary	
2010/0089395	A1	4/2010	Power	
2010/0218759	A1	9/2010	Anderson	
2011/0041845	A1	2/2011	Solomon	
2012/0006322	A1	1/2012	Anderson	

FOREIGN PATENT DOCUMENTS

EP	1486227	12/2004
GB	2320489	6/1998
JP	02502129	7/1990
JP	450059	8/1992
JP	07100205	4/1995
JP	10504220	4/1998
JP	2002528144	9/2002
JP	2004501685	1/2004
JP	2008-94103 A	4/2008
JP	2008094103	4/2008
JP	2008261423	10/2008
JP	2009233308	10/2009
JP	2009257392	11/2009
JP	2010096308	4/2010
WO	8909078	10/1989
WO	9628205	9/1996
WO	9828033	7/1998
WO	9936115	7/1999
WO	02/00281 A2	1/2002
WO	03101514	12/2003
WO	2005102430	11/2005
WO	2006062449	6/2006
WO	2006062449 A1	6/2006
WO	2007012861	2/2007
WO	2007062518	6/2007
WO	2008023019	2/2008
WO	2008119552	2/2008
WO	2011012325	2/2011
WO	2011012327	2/2011

OTHER PUBLICATIONS

Advisory Action dated Mar. 13, 2017 for U.S. Appl. No. 14/699,567.
Non-Final Office Action dated Jan. 12, 2017 for U.S. Appl. No. 14/713,620, 8 pages.
Final Rejection dated Sep. 27, 2016 for U.S. Appl. No. 14/699,578.
Final Office Action dated Aug. 31, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Advisory action dated Feb. 9, 2017 for U.S. Appl. No. 14/699,584.
Non-final rejection dated Jul. 12, 2016 for U.S. Appl. No. 14/713,643.
File History for U.S. Appl. No. 15/271,738.
File History for U.S. Appl. No. 15/269,102.
File History for U.S. Appl. No. 15/262,818.
File History for U.S. Appl. No. 15/289,553.
File History for U.S. Appl. No. 15/269,249.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/699,584.
Non-Final Office Action dated Jun. 24, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/713,631.
Advisory Action dated Mar. 16, 2017 or U.S. Appl. No. 14/713,633.
Entire patent prosecution history of U.S. Appl. No. 13/110,532, filed May 18, 2011, entitled,"Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,324, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,343, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,353, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,363, filed Dec. 1, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/103,392, filed Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/699,567, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler and Method for Counting Doses."
Entire patent prosecution history of U.S. Appl. No. 14/699,578, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having a Bore and Shaft Arrangement."
Entire patent prosecution history of U.S. Appl. No. 14/699,584, filed Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having an Antireverse Rotation Actuator".

(56) **References Cited**

OTHER PUBLICATIONS

Entire patent prosecution history of U.S. Appl. No. 14/713,612, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/713,620, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
Entire patent prosecution history of U.S. Appl. No. 14/713,643, filed May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof."
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 211.8.
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 212.6.
First Examination Report of counterpart New Zealand Patent Application No. 603466, dated Jul. 1, 2013.

* cited by examiner

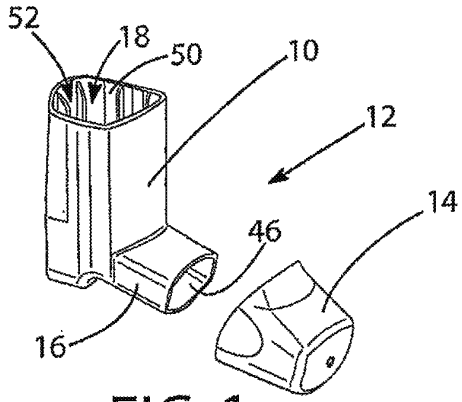


FIG. 1

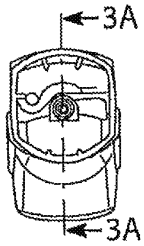


FIG. 2

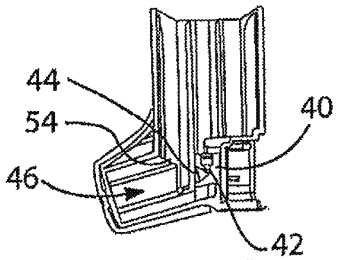


FIG. 3A

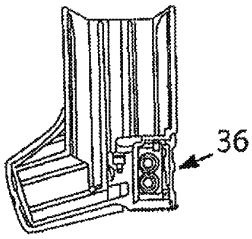


FIG. 3B

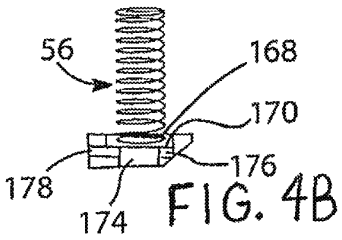


FIG. 4B

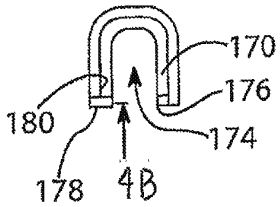


FIG. 4C

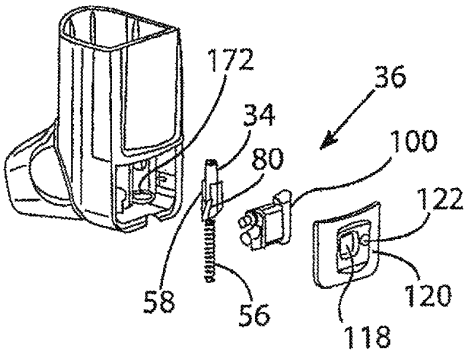


FIG. 4A

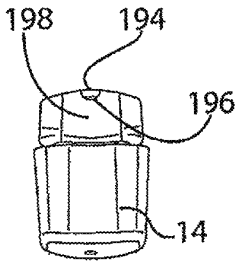


FIG. 5

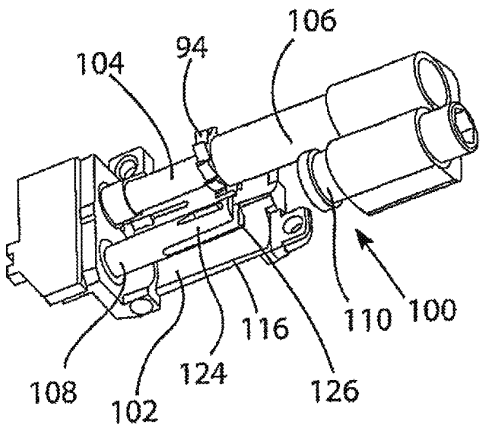


FIG. 6A

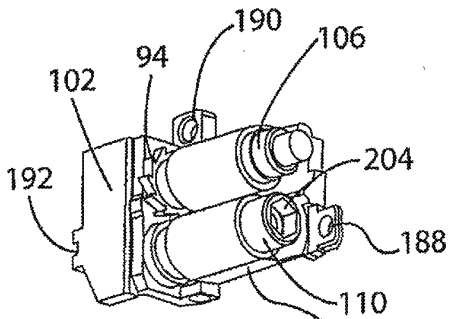


FIG. 6B

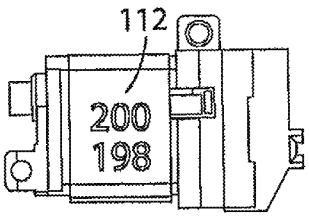


FIG. 6C

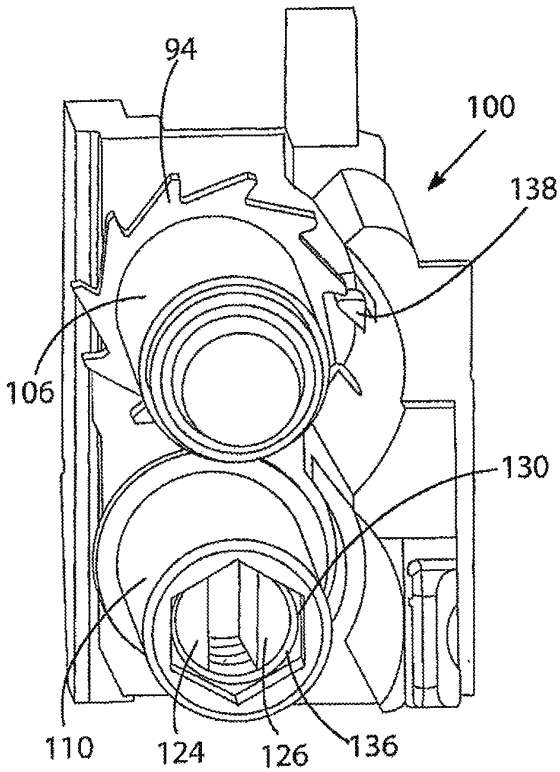


FIG. 6D

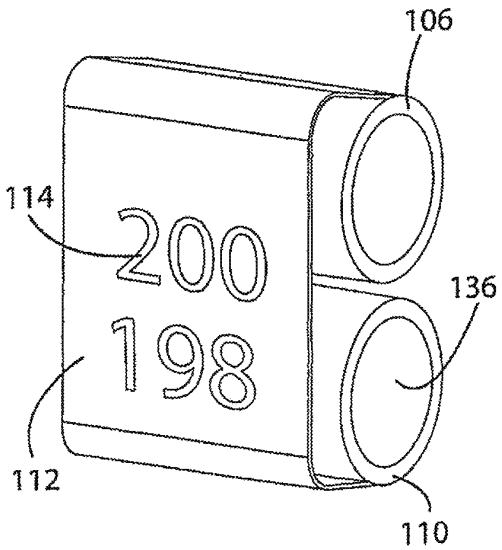


FIG. 6E

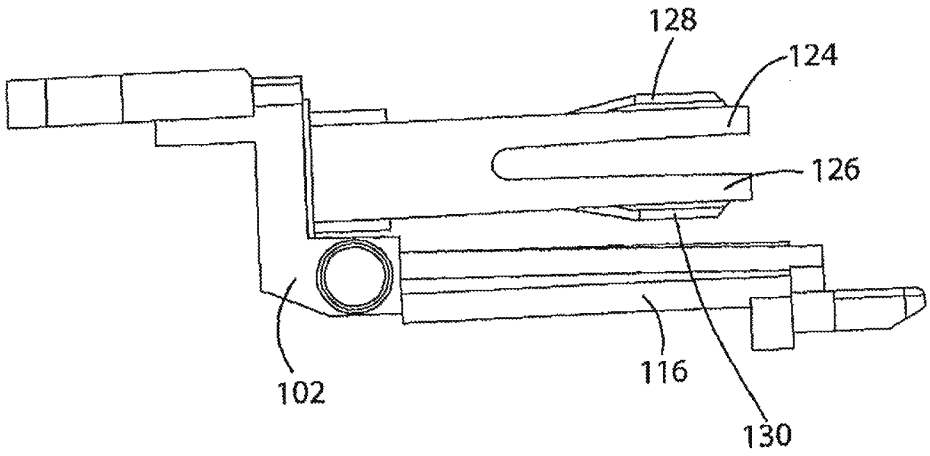


FIG. 6F

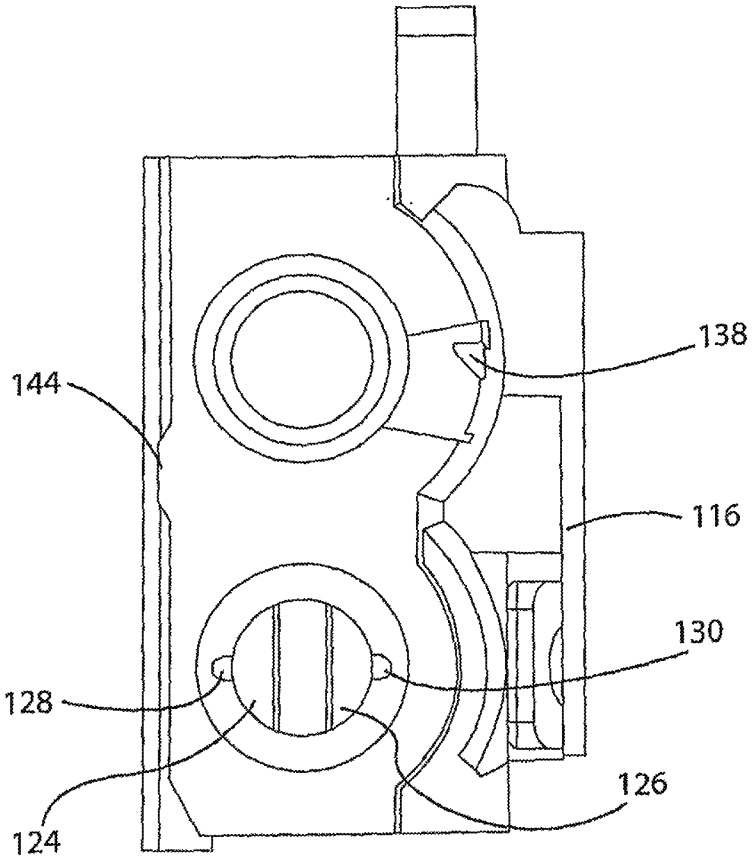


FIG. 6G

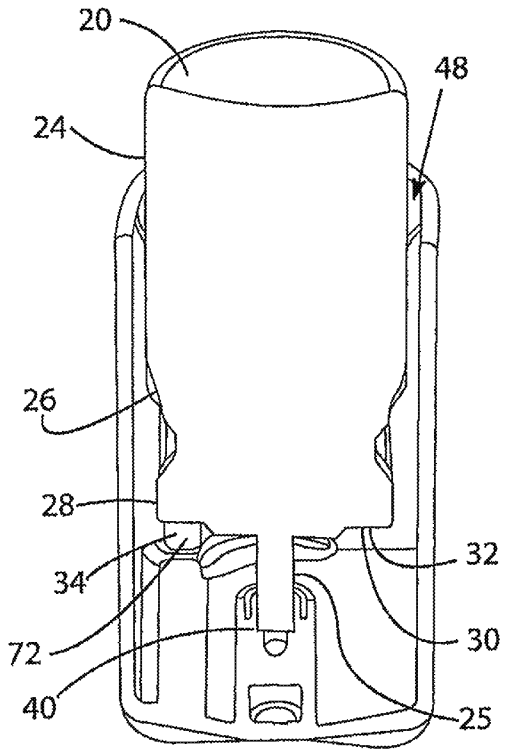


FIG. 7A

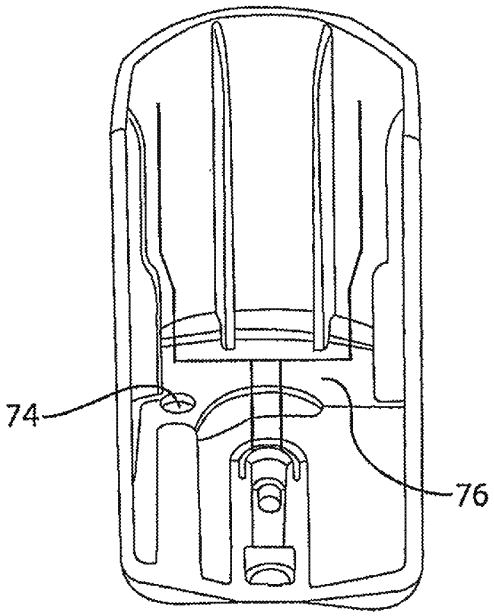


FIG. 7B

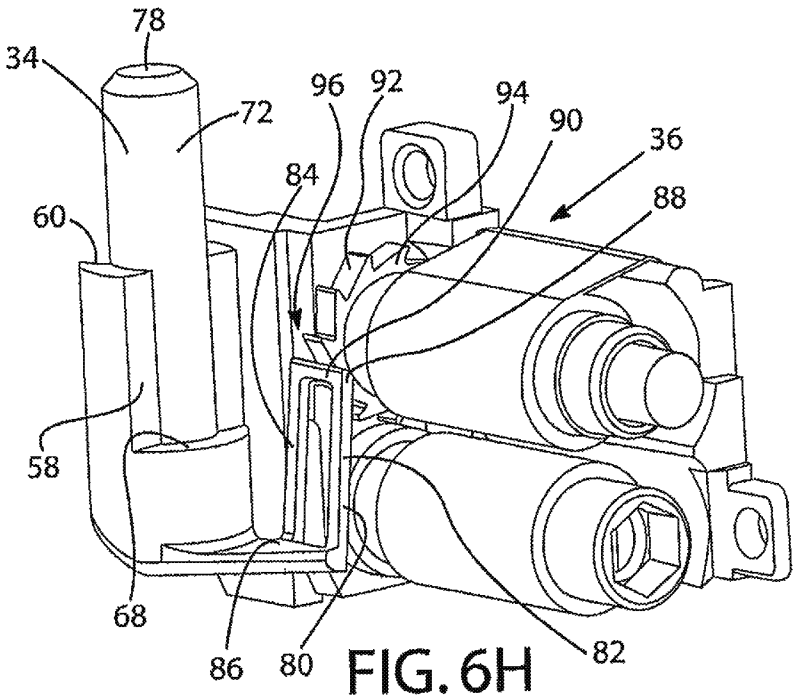


FIG. 6H

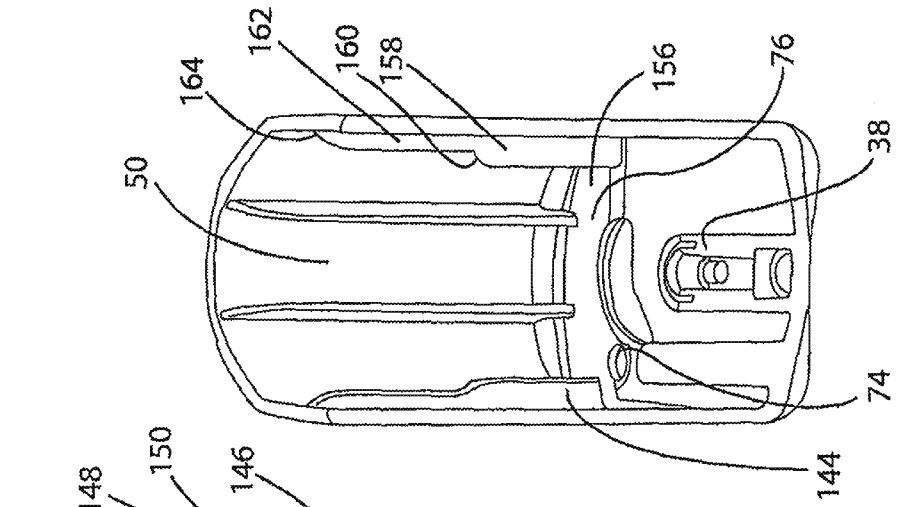


FIG. 7C

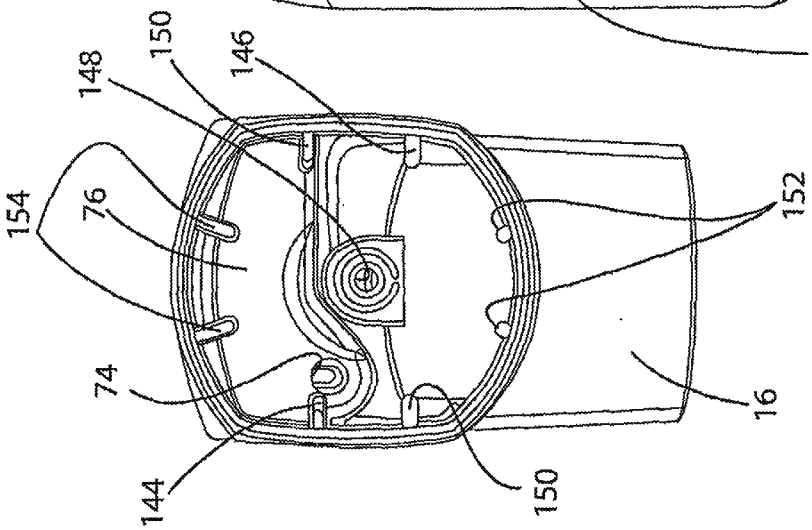


FIG. 7D

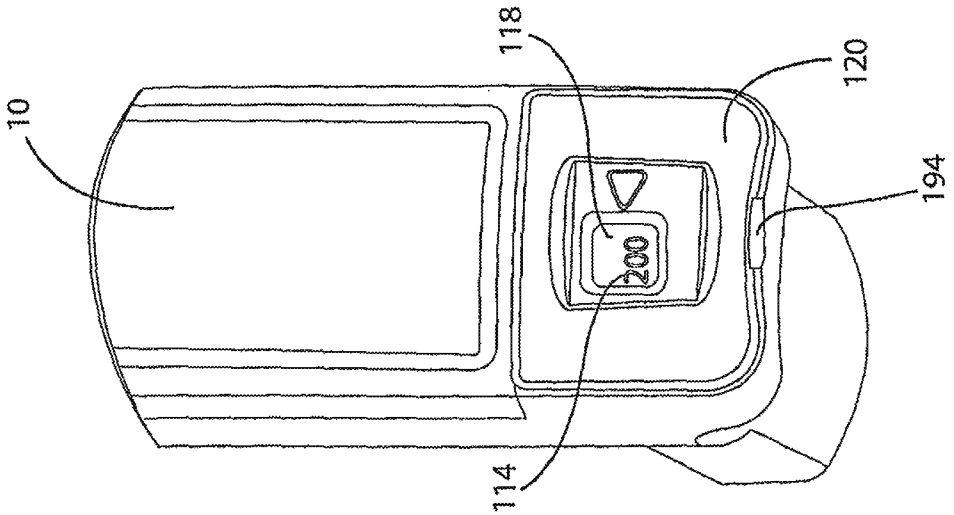


FIG. 8D

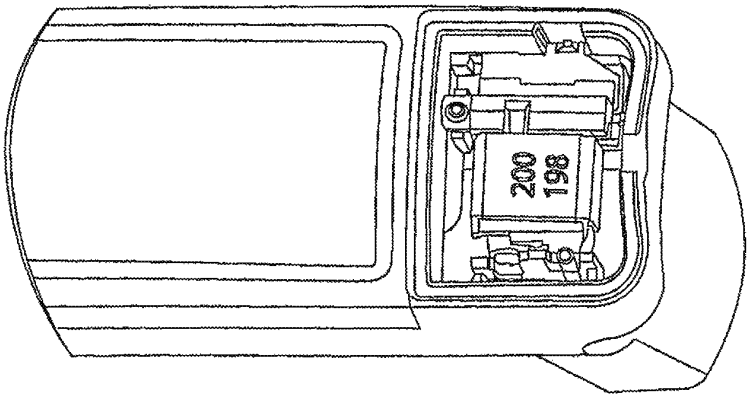


FIG. 8C

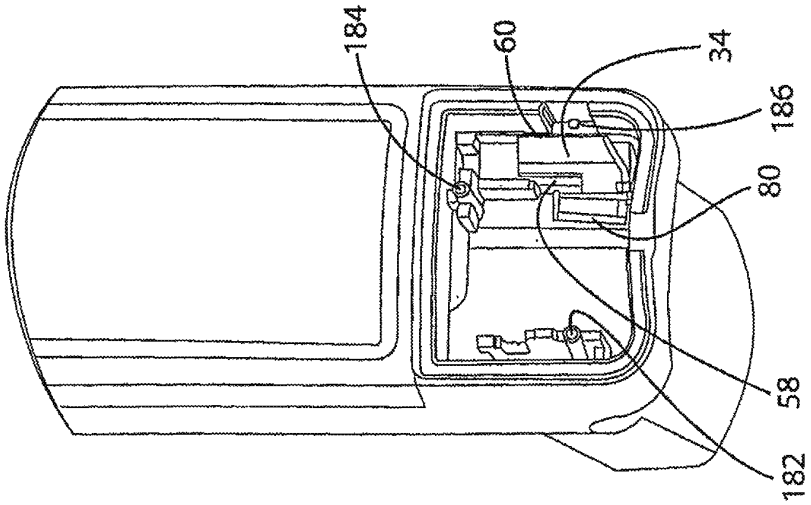


FIG. 8B

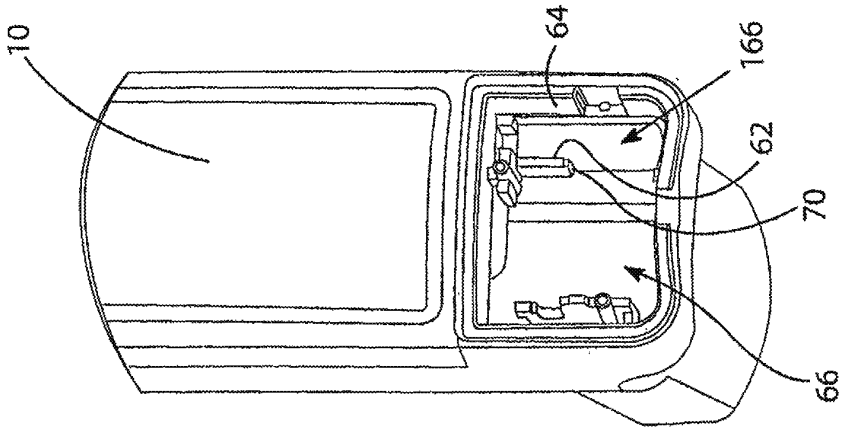


FIG. 8A

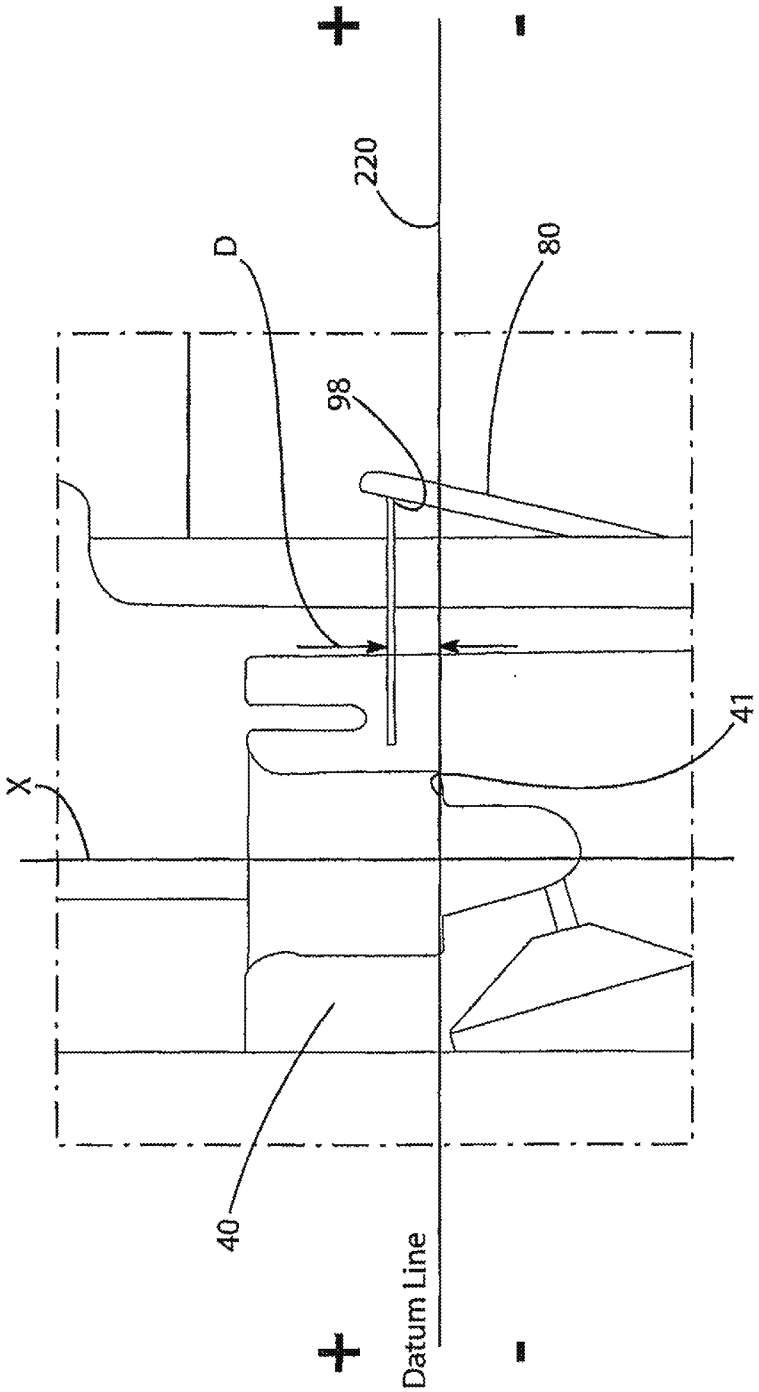


FIG. 9

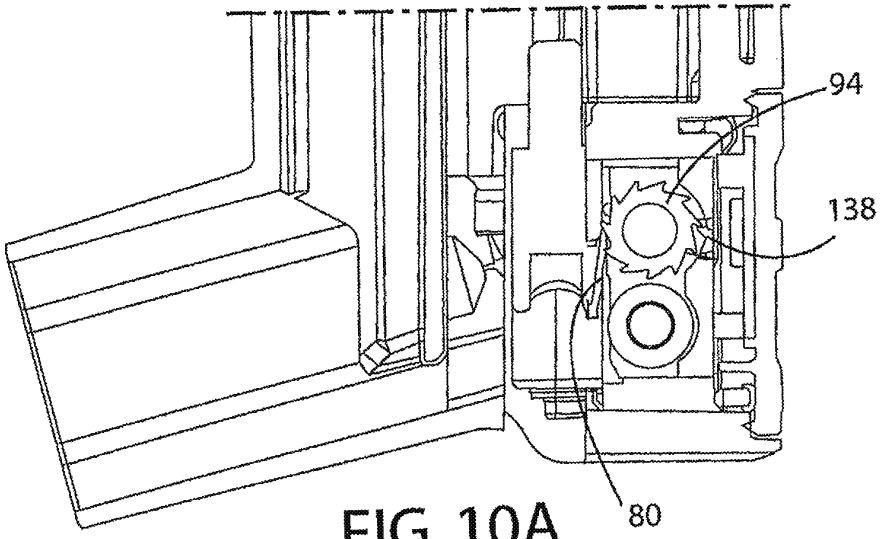


FIG. 10A

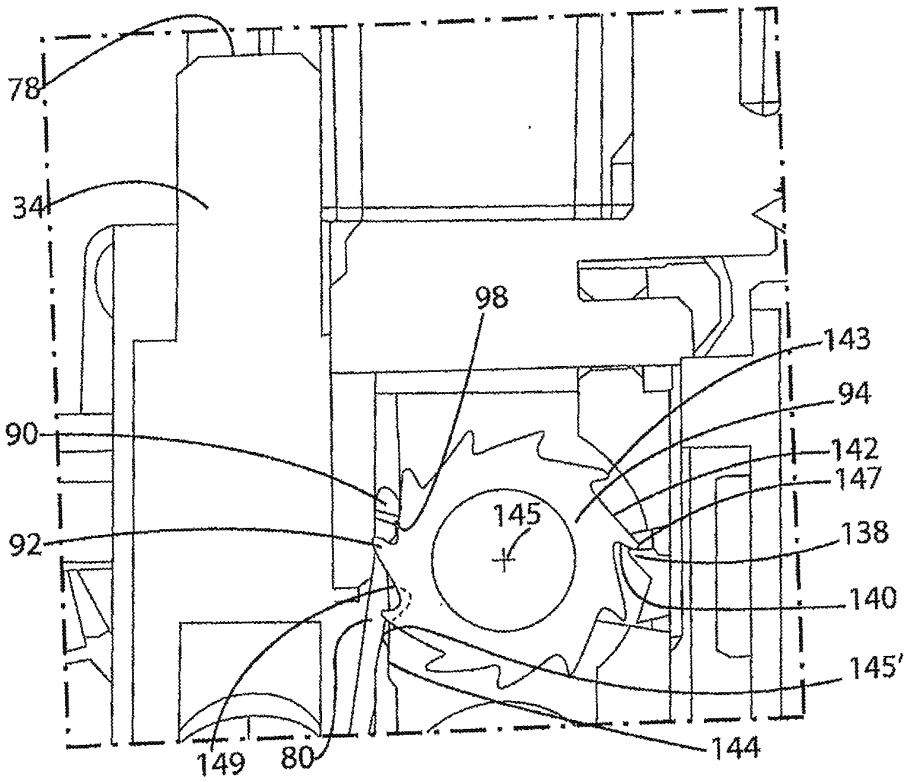


FIG. 10B

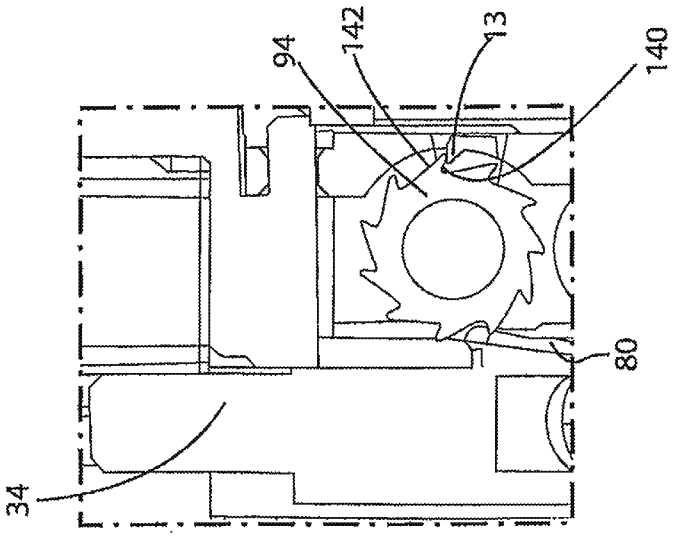


FIG. 10E

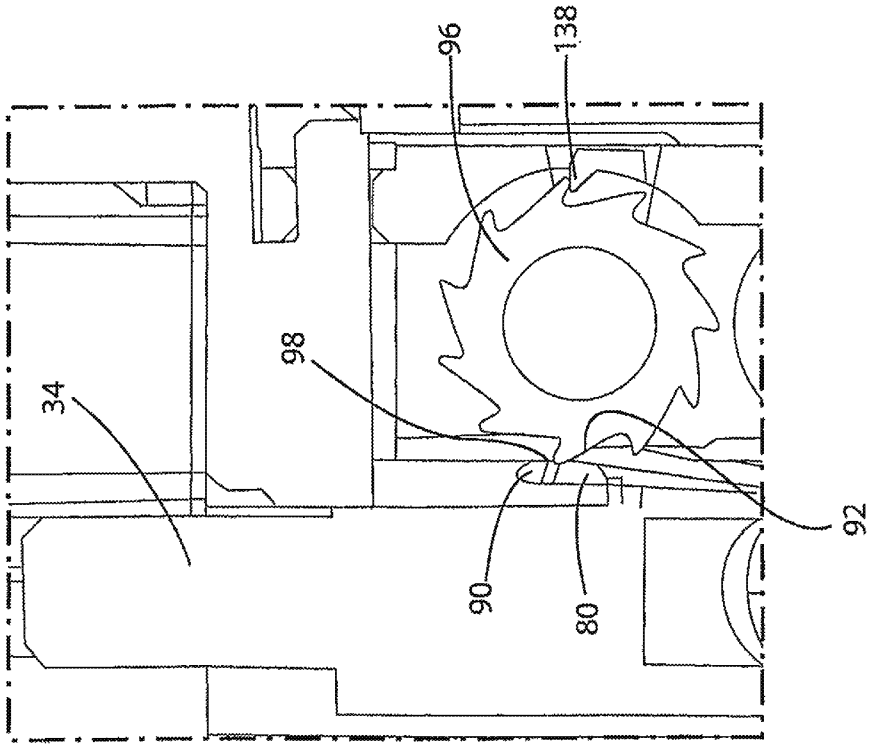


FIG. 10C

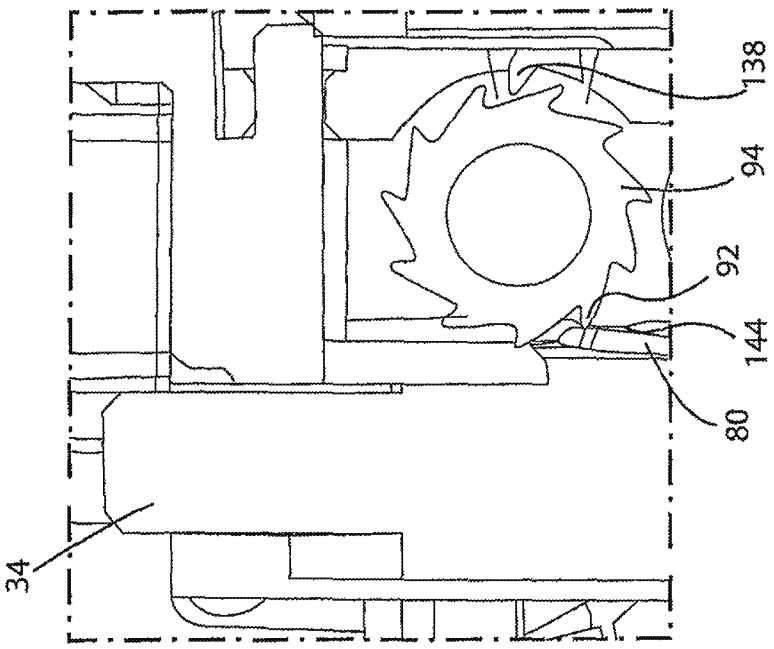


FIG. 10F

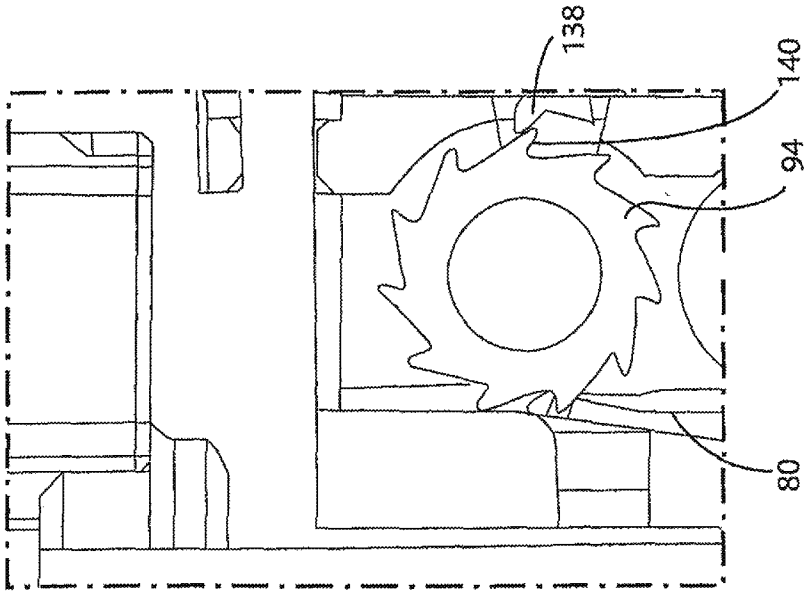


FIG. 10D

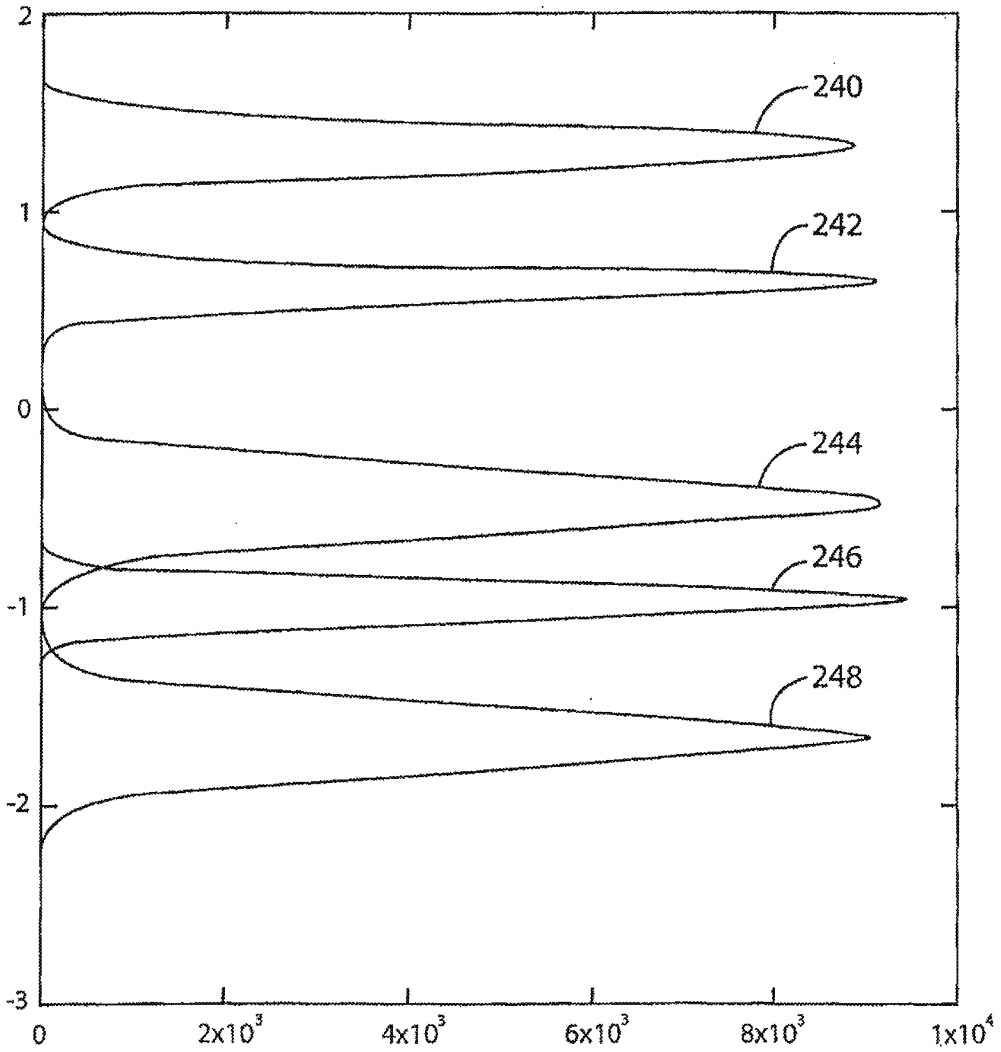

2
1
0
-1
-2
-3
240
242
244
246
248
0
2x10^3
4x10^3
6x10^3
8x10^3
1x10^4

FIG. 11

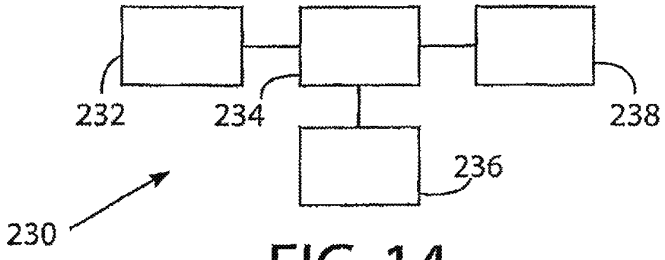

232
234
238
236
230

FIG. 14

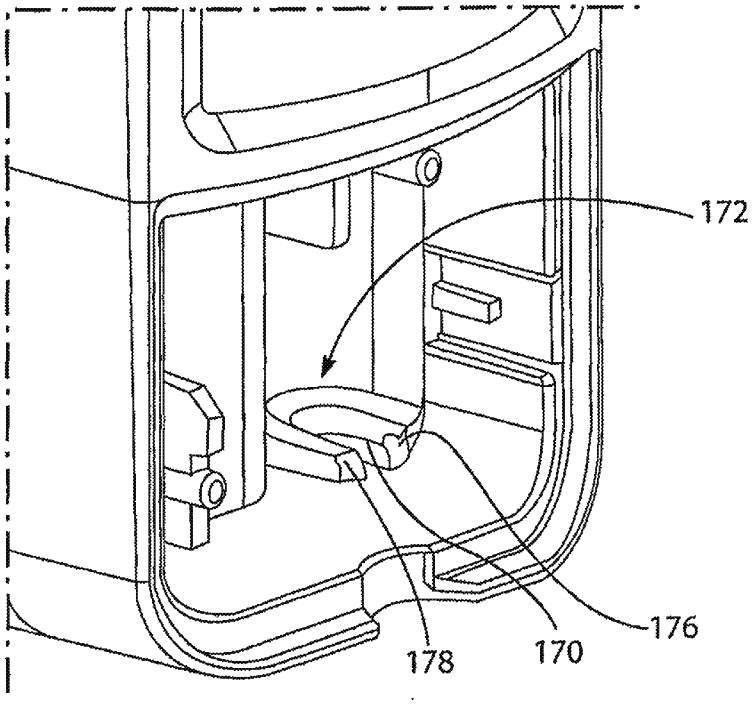
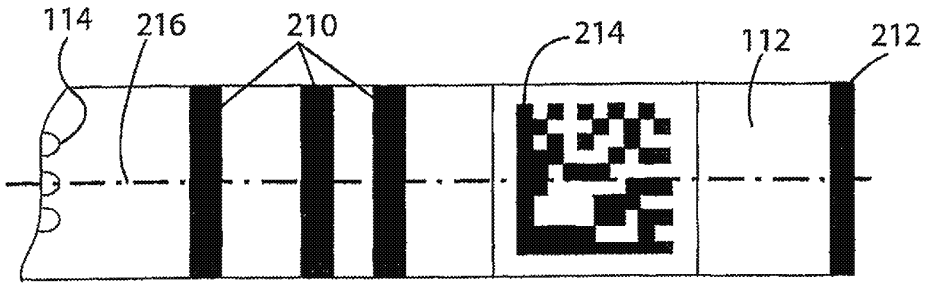


FIG. 12



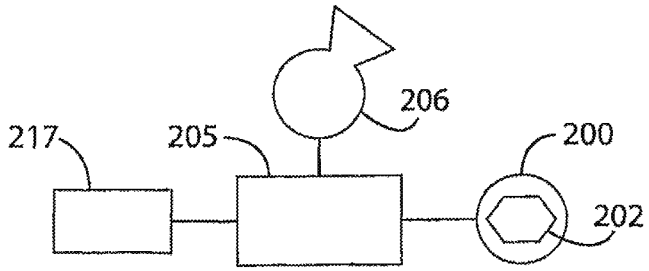


FIG. 13

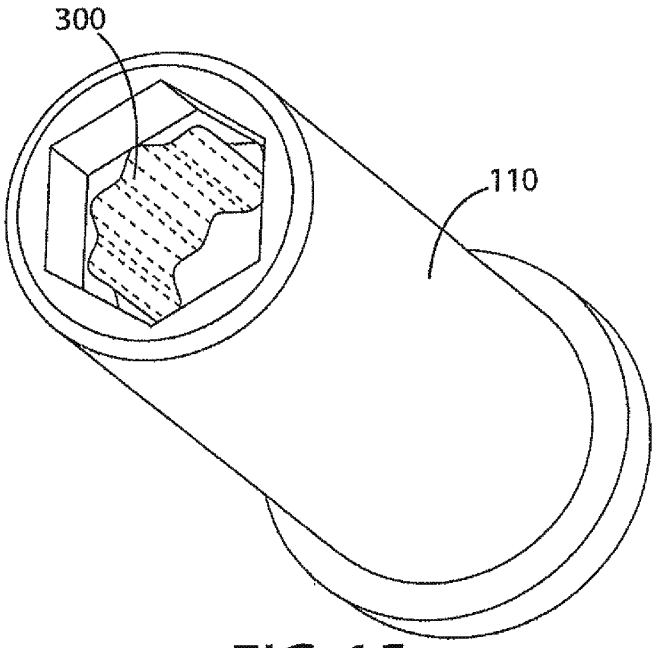


FIG. 15

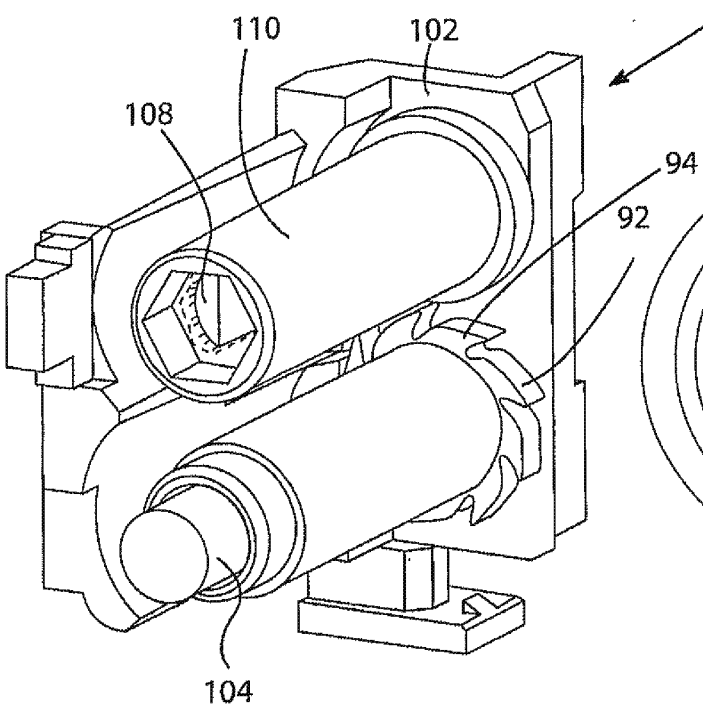


FIG. 20

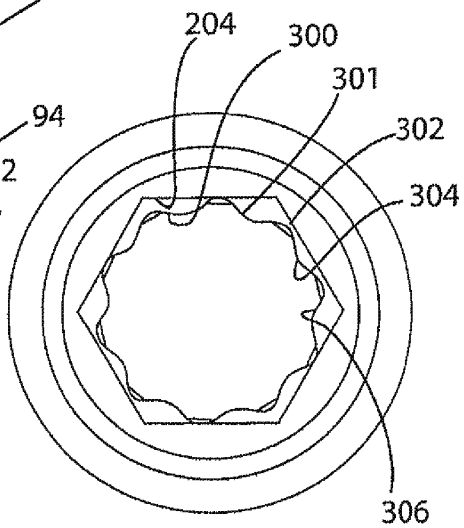


FIG. 16

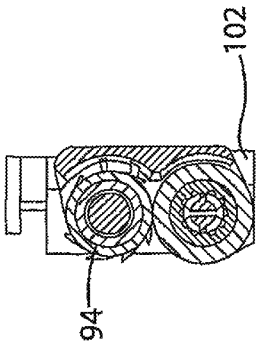


FIG. 19A

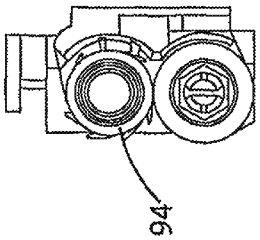


FIG. 19B

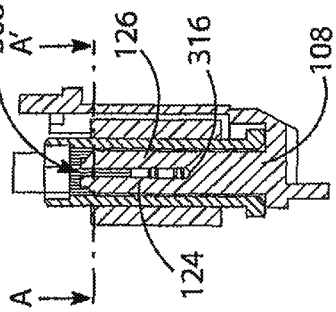


FIG. 19C

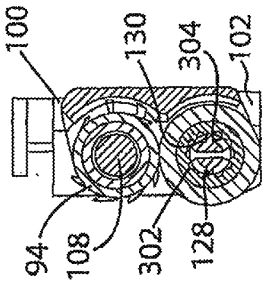


FIG. 18A

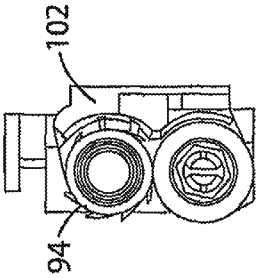


FIG. 18B

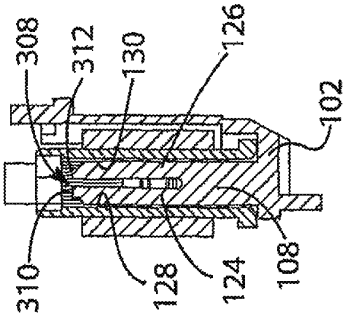


FIG. 18C

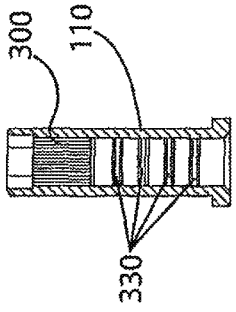


FIG. 17

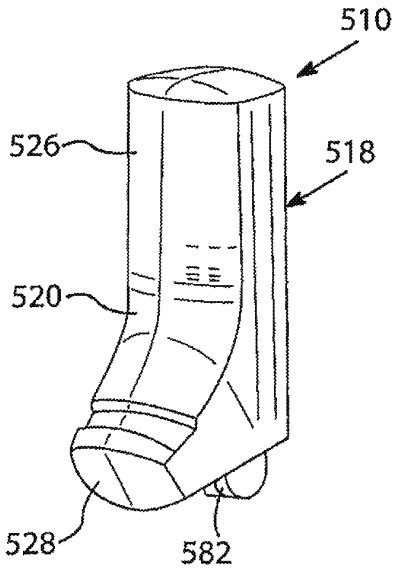

510
526
518
520
528
582

FIG. 21

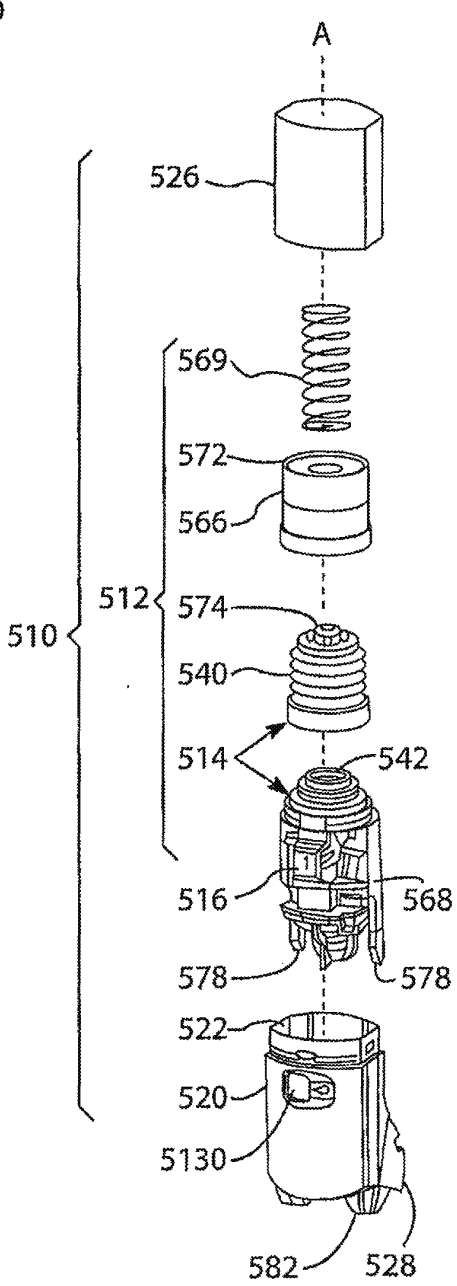

A
526
569
572
566
512
574
510
540
514
542
516
568
578
578
522
520
5130
582
528

FIG. 22

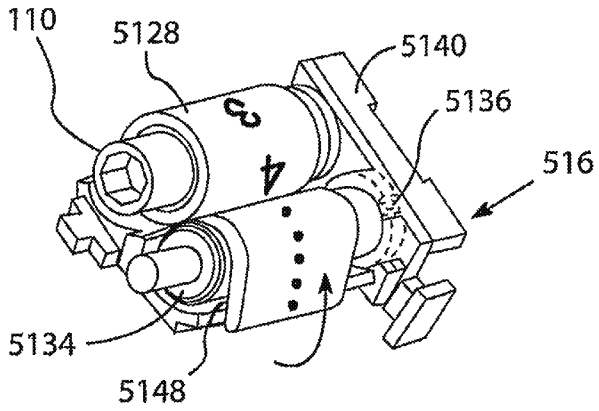

110
5128
5140
5136
516
5134
5148

FIG. 23

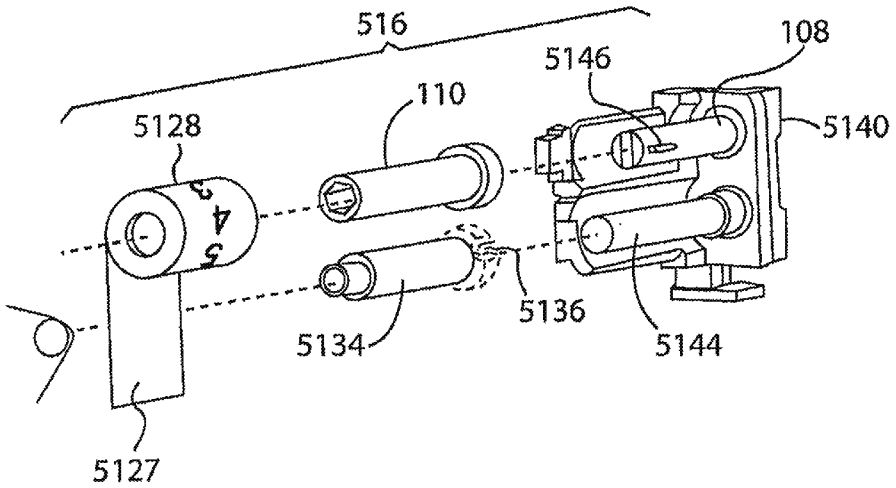

516
108
5146
110
5128
5140
5136
5134
5144
5127

FIG. 24

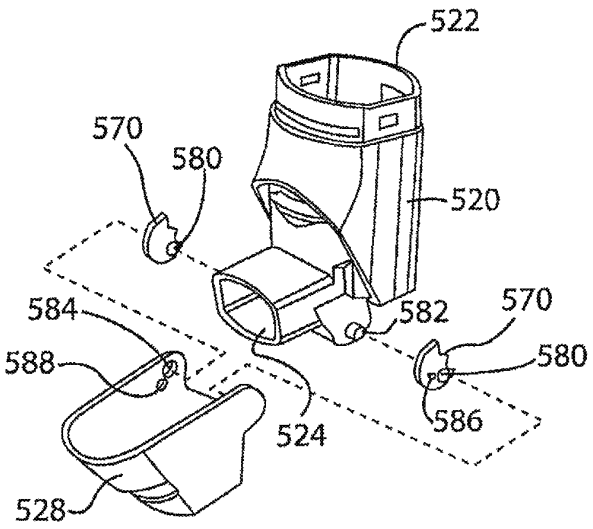


FIG. 25

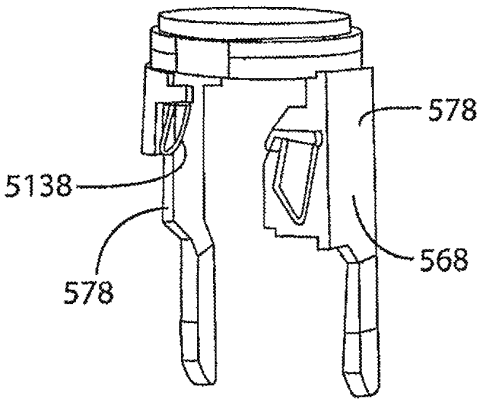


FIG. 26

DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation patent application of U.S. Non-Provisional patent application Ser. No. 14/699,584, filed Apr. 29, 2015, which is a continuation patent application of U.S. Non-Provisional patent application Ser. No. 14/103,353, filed Dec. 11, 2013, which is a divisional patent application of U.S. Non-Provisional patent application Ser. No. 13/110,532, filed May 18, 2011, now U.S. Pat. No. 8,978,966, issued Mar. 17, 2015, which claims priority to U.S. Provisional Patent Application No. 61/345,763, filed May 18, 2010, and U.S. Provisional Patent Application No. 61/417,659, filed Nov. 29, 2010, each of which is incorporated herein by reference in its entirety for any and all purposes.

FIELD OF THE INVENTION

The present invention relates to dose counters for inhalers, inhalers and methods of assembly thereof. The invention is particularly applicable to metered dose inhalers including dry power medicament inhalers, breath actuated inhalers and manually operated metered dose medicament inhalers.

BACKGROUND OF THE INVENTION

Metered dose inhalers can comprise a medicament-containing pressurised canister containing a mixture of active drug and propellant. Such canisters are usually formed from a deep-dawn aluminium cup having a crimped lid which carries a metering valve assembly. The metering valve assembly is provided with a protruding valve stem which, in use is inserted as a push fit into a stem block in an actuator body of an inhaler having a drug delivery outlet. In order to actuate a manually operable inhaler, the user applies by hand a compressive force to a closed end of the canister and the internal components of the metering valve assembly are spring loaded so that a compressive force of approximately 15 to 30N is required to activate the device in some typical circumstances.

In response to this compressive force the canister moves axially with respect to the valve stem and the axial movement is sufficient to actuate the metering valve and cause a metered quantity of the drug and the propellant to be expelled through the valve stem. This is then released into a mouthpiece of the inhaler via a nozzle in the stem block, such that a user inhaling through the outlet of the inhaler will receive a dose of the drug.

A drawback of self-administration from an inhaler is that it is difficult to determine how much active drug and/or propellant are left in the inhaler, if any, especially of the active drug and this is potentially hazardous for the user since dosing becomes unreliable and backup devices not always available.

Inhalers incorporating dose counters have therefore become known.

WO 98/028033 discloses an inhaler having a ratchet mechanism for driving a tape drive dose counter. A shaft onto which tape is wound has a friction clutch or spring for restraining the shaft against reverse rotation.

EP-A-1486227 discloses an inhaler for dry powered medicament having a ratchet mechanism for a tape dose counter which is operated when a mouthpiece of the inhaler

is closed. Due to the way in which the mouthpiece is opened and closed, and actuation pawl of the device which is mounted on a yoke, travels a known long stroke of consistent length as the mouthpiece is opened and closed.

WO 2008/119552 discloses a metered-dose inhaler which is suitable for breath-operated applications and operates with a known and constant canister stroke length of 3.04 mm+/−0.255 mm. A stock bobbin of the counter, from which a tape is unwound, rotates on a shaft having a split pin intended to hold the stock bobbin taut. However, some dose counters do not keep a particularly reliable count, such as if they are dropped onto a hard surface.

More recently, it has become desirable to improve dose counters further and, in particular, it is felt that it would be useful to provide extremely accurate dose counters for manually-operated canister-type metered dose inhalers. Unfortunately, in these inhalers, it has been found in the course of making the present invention that the stroke length of the canister is to a very large extent controlled on each dose operation by the user, and by hand. Therefore, the stroke length is highly variable and it is found to be extremely difficult to provide a highly reliable dose counter for these applications. The dose counter must not count a dose when the canister has not fired since this might wrongly indicate to the user that a dose has been applied and if done repeatedly the user would throw away the canister or whole device before it is really time to change the device due to the active drug and propellant reaching a set minimum. Additionally, the canister must not fire without the dose counter counting because the user may then apply another dose thinking that the canister has not fired, and if this is done repeatedly the active drug and/or propellant may run out while the user thinks the device is still suitable for use according to the counter. It has also been found to be fairly difficult to assembly some known inhaler devices and the dose counters therefor. Additionally, it is felt desirable to improve upon inhalers by making them easily usable after they have been washed with water.

The present invention aims to alleviate at least to a certain extent one or more of the problems of the prior art.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a counter display arranged to indicate dosage information, a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

The regulator is advantageous in that it helps prevent unwanted motion of the counter display if the counter is dropped.

According to a further aspect of the present invention, the regulator provides a resistance force of greater than 0.1 N against movement of the counter display. According to still a further aspect of the present invention, the resistance force is greater than 0.3 N. According to yet a further aspect of the present invention, the resistance force is from 0.3 to 0.4 N.

Preferably, the counter comprises a tape.

Preferably, the tape has dose counter indicia displayed thereon. The first station may comprise a region of the dose counter where tape is held which is located before a display location, such as a display window, for the counter indicia.

The first station may comprise a first shaft, the tape being arranged on the first shaft and to unwind therefrom upon movement of the counter display.

The first shaft may be mounted for rotation relative to a substantially rotationally fixed element of the dose counter.

The regulator may comprise at least one projection which is arranged on one of the first shaft and the substantially rotationally fixed element and to engage incrementally with one or more formations on the other of the first shaft and the substantially rotationally fixed element.

At least two said projections may be provided. Exactly two said projections maybe provided.

Each projection may comprise a radiused surface.

The at least one projection may be located on the substantially fixed element which may comprise a fixed shaft which is fixed to a main body of the dose counter, the first shaft being rotationally mounted to the fixed shaft.

Preferably, the fixed shaft has at least two resiliently flexible legs (or forks). Each leg may have at least one said projection formed in an outwardly facing direction thereon, said one or more formations being formed on an inwardly facing engagement surface of the first shaft, said at least one projection being arranged to resiliently engage said one or more formations. Preferably, a series of said formations are provided. An even number of said formations may be provided. Eight to twelve of said formations may be provided. In one embodiment, ten said formations are provided.

Each said formation may comprise a concavity formed on an engagement surface. Each concavity may comprise a radiused surface wall portion which preferably merges on at least one side thereof into a flat wall portion surface. The engagement surface may include a series of said concavities, and convex wall portions of the engagement surface may be formed between each adjacent two said concavities, each said convex wall portion comprising a convex radiused wall portion.

Each convex radiused wall portion of each convex wall portion may be connected by said flat wall portion surfaces to each adjacent concavity.

The fixed shaft may comprise a split pin with fork legs and each projection may be located on a said fork leg.

The first shaft may comprise a substantially hollow bobbin.

Said at least one formation may be located on an inner surface of the bobbin. In other embodiments it may be located on an outer surface thereof. Said engagement surface may extend partially along said bobbin, a remainder of the respective inner or outer surface having a generally smooth journal portion along at least a portion thereof.

The drive system may comprise a tooth ratchet wheel arranged to act upon a second shaft which is located at the second station, the second shaft being rotatable to wind the tape onto the second shaft.

The second shaft may be located on a main body of the dose counter spaced from and parallel to the first shaft.

The ratchet wheel may be fixed to the second shaft is arranged to rotate therewith. The ratchet wheel may be secured to an end of the second shaft and aligned coaxially with the second shaft.

The dose counter may include anti-back drive system which is arranged to restrict motion of the second shaft. The anti-back drive system may include a substantially fixed tooth arranged to act upon teeth of the ratchet wheel.

According to a further aspect of the present invention, a dose counter includes an anti-back drive system which is arranged to restrict motion of the second shaft in a tape winding direction.

According to a further aspect of the present invention there is provided a shaft for holding counter tape in a dose counter for an inhaler, the shaft having an engagement surface including incrementally spaced formations located around a periphery thereof, the formations comprising a series of curved concavities and convex portions.

The shaft may comprise a hollow bobbin.

The engagement surface may be a generally cylindrical inwardly directed surface.

The engagement surface may include a flat surface wall portion joining each concavity and convex wall portion.

Each concavity may comprise a radiused wall portion.

Each convex wall portion may comprise a radiused wall portion.

Said concavities may be regularly spaced around a longitudinal axis of the shaft.

Said convex wall portions may be regularly spaced around a longitudinal axis of the shaft.

In some embodiments there may be from eight to twelve said concavities and/or convex wall portions regularly spaced around a longitudinal axis thereof.

One embodiment includes ten said concavities and/or convex wall portions regularly spaced around a longitudinal axis of the shaft.

According to a further aspect of the present invention there is provided a shaft and counter tape assembly for use in a dose counter for an inhaler, the assembly comprising a rotatable shaft and a counter tape which is wound around the shaft and is adapted to unwind therefrom upon inhaler actuation, the shaft having an engagement surface which includes incrementally spaced formations located around a periphery thereof.

According to a further aspect of the present invention there is provided an inhaler for the inhalation of medication and the like, the inhaler including a dose counter as in the first aspect of the present invention.

A preferred construction consists of a manually operated metered dose inhaler including a dose counter chamber including a dose display tape driven by a ratchet wheel which is driven in turn by an actuator pawl actuated by movement of a canister, the tape unwinding from a stock bobbin during use of the inhaler, a rotation regulator being provided for the stock bobbin and comprising a wavelike engagement surface with concavities which engage against control elements in the form of protrusions on resilient forks of a split pin thereby permitting incremental unwinding of the stock bobbin yet resisting excessive rotation if the inhaler is dropped onto a hard surface.

According to another aspect of the present invention there is provided a dose counter for a metered dose inhaler having a body arranged to retain a medicament canister of predetermined configuration for movement of the canister relative thereto; the dose counter comprising: an incremental counting system for counting doses, the incremental counting system having a main body, an actuator arranged to be driven in response to canister motion and to drive an incremental output member in response to canister motion, the actuator and incremental output member being configured to have predetermined canister fire and count configurations in a canister fire sequence, the canister fire configuration being determined by a position of the actuator relative to a datum at which the canister fires medicament and the count configuration being determined by a position of the actuator relative to the datum at which the incremental count system makes an incremental count, wherein the actuator is

arranged to reach a position thereof in the count configuration at or after a position thereof in the canister fire configuration.

This arrangement has been found to be highly advantageous since it provides an extremely accurate dose counter which is suitable for use with manually operated metered dose inhalers. It has been found that dose counters with these features have a failure rate of less than 50 failed counts per million full canister activation depressions. It has been found in the course of making the present invention that highly reliable counting can be achieved with the dose counter counting at or soon after the point at which the canister fires. It has been is covered by the present inventors that momentum and motion involved in firing the canister, and in some embodiments a slight reduction in canister back pressure on the user at the time of canister firing, can very reliably result in additional further motion past the count point.

The actuator and incremental counting system may be arranged such that the actuator is displaced less than 1 mm, typically 0.25 to 0.75 mm, more preferably about 0.4 to 0.6 mm, relative to the body between its location in the count and fire configurations, about 0.48 mm being preferred. The canister, which can move substantially in line with the actuator, can reliably move this additional distance so as to achieve very reliable counting.

The incremental count system may comprise a ratchet mechanism and the incremental output member may comprise a ratchet wheel having a plurality of circumferentially spaced teeth arranged to engage the actuator.

The actuator may comprise an actuator pawl arranged to engage on teeth of the ratchet wheel. The actuator pawl may be arranged to be connected to or integral with an actuator pin arranged to engage and be depressed by a medicament canister bottom flange. The actuator pawl may be generally U-shaped having two parallel arms arranged to pull on a central pawl member arranged substantially perpendicular thereto. This provides a very reliable actuator pawl which can reliably pull on the teeth of the ratchet wheel.

The incremental count system may include a tape counter having tape with incremental dose indicia located thereon, the tape being positioned on a tape stock bobbin and being arranged to unwind therefrom.

The actuator and incremental output member may be arranged to provide a start configuration at which the actuator is spaced from the ratchet output member, a reset configuration at which the actuator is brought into engagement with the incremental output member during a canister fire sequence, and an end configuration at which the actuator disengages from the ratchet output during a canister fire sequence.

The actuator may be arranged to be located about 1.5 to 2.0 mm, from its location in the fire configuration, when in the start configuration, about 1.80 mm being preferred.

The actuator may be arranged to be located about 1.0 to 1.2 mm, from its location in the fire configuration, when in the reset configuration, about 1.11 mm being preferred.

The actuator may be arranged to be located about 1.1 to 1.3 mm, from its location in the fire configuration, when in the end configuration, about 1.18 mm being preferred.

These arrangements provide extremely reliable dose counting, especially with manually operated canister type metered dose inhalers.

The main body may include a formation for forcing the actuator to disengage from the incremental output member when the actuator is moved past the end configuration. The formation may comprise a bumped up portion of an otherwise generally straight surface against which the actuator engages and along which it is arranged to slide during a canister firing sequence.

The dose counter may include a counter pawl, the counter pawl having a tooth arranged to engage the incremental output member, the tooth and incremental output member being arranged to permit one way only incremental relative motion therebetween. When the incremental output member comprises a ratchet wheel, the tooth can therefore serve as an anti-back drive tooth for the ratchet wheel, thereby permitting only one way motion or rotation thereof.

The counter pawl may be substantially fixedly mounted on the main body of the incremental count system and the counter pawl may be arranged to be capable of repeatedly engaging equi-spaced teeth of the incremental output member in anti-back drive interlock configurations as the counter is operated. The counter pawl may be positioned so that the incremental output member is halfway, or substantially halfway moved from one anti-back drive interlock configuration to the next when the actuator and incremental output member are in the end configuration thereof. This is highly advantageous in that it minimises the risk of double counting or non-counting by the dose counter.

According to a further aspect of the invention there is provided an inhaler comprising a main body arranged to retain a medicament canister of predetermined configuration and a dose counter mounted in the main body.

The inhaler main body may include a canister receiving portion and a separate counter chamber, the dose counter being located within the main body thereof, the incremental output member and actuator thereof inside the counter chamber, the main body of the inhaler having wall surfaces separating the canister-receiving portion and the counter chamber, the wall surfaces being provided with a communication aperture, an actuation member extending through the communication aperture to transmit canister motion to the actuator.

According to a further aspect of the present invention there is a provided an inhaler for metered dose inhalation, the inhaler comprising a main body having a canister housing arranged to retain a medicament canister for motion therein, and a dose counter, the dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of a medicament canister, wherein the canister housing has an inner wall, and a first inner wall canister support formation located directly adjacent the actuation member.

This is highly advantageous in that the first inner wall canister support formation can prevent a canister from rocking too much relative to the main body of the inhaler. Since the canister may operate the actuation member of the dose counter, this substantially improves dose counting and avoids counter errors.

The canister housing may have a longitudinal axis which passes through a central outlet port thereof, the central outlet port being arranged to mate with an outer canister fire stem of a medicament canister, the inner wall canister support formation, the actuation member and the outlet port lying in a common plane coincident with the longitudinal axis. Accordingly, this construction may prevent the canister from rocking towards the position of the dose counter actuation member, thereby minimising errors in counting.

The canister housing may have a further inner canister wall support formation located on the inner wall opposite, or substantially opposite, the actuation member. Accordingly, the canister may be supported against rocking motion away from the actuator member so as to minimise count errors.

The canister housing may be generally straight and tubular and may have an arrangement in which each said inner wall support formation comprises a rail extending longitudinally along the inner wall.

Each said rail may be stepped, in that it may have a first portion located towards a medicine outlet end or stem block of the canister housing which extends inwardly a first distance from a main surface of the inner wall and a second portion located toward an opposite end of the canister chamber which extends inwardly a second, smaller distance from the main surface of the inner wall. This may therefore enable easy insertion of a canister into the canister housing such that a canister can be lined up gradually in step wise function as it is inserted into the canister housing.

The inhaler may include additional canister support rails which are spaced around an inner periphery of the inner wall of the canister housing and which extend longitudinally therealong.

At least one of the additional rails may extend a constant distance inwardly from the main surface of the inner wall.

At least one of the additional rails may be formed with a similar configuration to the first inner wall canister support formation.

The dose counter may, apart from said at least a portion of the actuation member, be located in a counter chamber separate from the canister housing, the actuation member comprising a pin extending through an aperture in a wall which separates the counter chamber and the canister housing.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicaments having: a body for retaining a medicament store; the body including a dose counter, the dose counter having a moveable actuator and a return spring for the actuator, the return spring having a generally cylindrical and annular end; the body having a support formation therein for supporting said end of the return spring, the support formation comprising a shelf onto which said end is engageable and a recess below the shelf.

This shelf and recess arrangement is highly advantageous since it allows a tool (such as manual or mechanical tweezers) to be used to place the return spring of the actuator onto the shelf with the tool then being withdrawn at least partially via the recess.

The shelf may be U-shaped.

The support formation may include a U-shaped upstanding wall extending around the U-shaped shelf, the shelf and upstanding wall thereby forming a step and riser of a stepped arrangement.

The recess below the shelf my also be U-shaped.

At least one chamfered surface may be provided at an entrance to the shelf. This may assist in inserting the actuator and return spring into position.

A further aspect of the invention provides a method of assembly of an inhaler which includes the step of locating said end of said spring on the shelf with an assembly tool and then withdrawing the assembly tool at least partly via the recess. This assembly method is highly advantageous compared to prior art methods in which spring insertion has been difficult and in which withdrawal of the tool has sometimes accidentally withdrawn the spring again.

The cylindrical and annular end of the spring may be movable in a direction transverse to its cylindrical extent into the shelf while being located thereon.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament, the inhaler having a body for retaining a medicament store; and a dose counter, the dose counter having a moveable actuator and a chassis mounted on the body; the chassis being heat staked in position on the body. This is be highly advantageous in that the chassis can be very accurately positioned and held firmly in place, thereby further improving counting accuracy compared to prior art arrangements in which some movement of the chassis relative to the body may be tolerated in snap-fit connections.

The chassis may have at least one of a pin or aperture heat staked to a respective aperture or pin of the body.

The chassis may have a ratchet counter output member mounted thereon.

The ratchet counter output member may comprise a ratchet wheel arranged to reel in incrementally a dose meter tape having a dosage indicia located thereon.

According to a further aspect of the present invention there is provided a method of assembling an inhaler including the step of heat staking the chassis onto the body. The step of heat staking is highly advantageous in fixedly positioning the chassis onto the body in order to achieve highly accurate dose counting in the assembled inhaler.

The method of assembly may include mounting a spring-returned ratchet actuator in the body before heat staking the chassis in place. The method of assembly may include pre-assembling the chassis with a dose meter tape prior to the step of heat staking the chassis in place. The method of assembly may include attaching a dose meter cover onto the body after the heat staking step. The cover may be welded onto the body or may in some embodiments be glued or otherwise attached in place.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament and having a body, the body have a main part thereof for retaining a medicament store; and a dose counter, the dose counter being located in a dose counter chamber of the body which is separated from the main part of the body, the dose counter chamber of the body having a dosage display and being perforated so as to permit the evaporation of water or aqueous matter in the dose counter chamber into the atmosphere.

This is high advantageous since it enables the inhaler to be thoroughly washed and the dose counting chamber can thereafter dry out fully.

The display may comprise a mechanical counter display inside the dose counter chamber and a window for viewing the mechanical counter display. The mechanical counter display may comprise a tape. The perforated dose counter chamber may therefore enable reliable washing of the inhaler, if desired by the user, and may therefore dry out without the display window misting up.

The dose counter chamber may be perforated by a drain hole formed through an outer hole of the body. The drain hole may be located at a bottom portion of the body of the inhaler, thereby enabling full draining of the inhaler to be encouraged after washing when the inhaler is brought into an upright position.

According to a further aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a display tape arranged to be incrementally driven from a tape stock bobbin onto an incremental tape take-up drive shaft, the bobbin having an internal bore supported by and for rotation about a support shaft, at least one of the bore and support shaft having a protrusion which is resiliently biased into frictional engagement with the other of the bore and support shaft with longitudinally extending mutual frictional interaction. This arrangement may provide good friction for the bobbin, thereby improving tape counter

display accuracy and preventing the bobbin from unwinding undesirably for example if the inhaler is accidentally dropped.

The support shaft may be forked and resilient for resiliently biasing the support shaft and bore into frictional engagement.

The support shaft may have two forks, or more in some cases, each having a radially extending protrusion having a friction edge extending therealong parallel to a longitudinal axis of the support shaft for frictionally engaging the bore of the support shaft with longitudinally extending frictional interaction therebetween.

The bore may be a smooth circularly cylindrical or substantially cylindrical bore.

Each of the above inhalers in accordance with aspects of the present invention may have a medicament canister mounted thereto.

The canister may comprise a pressurised metered dose canister having a reciprocally movable stem extending therefrom and movable into a main canister portion thereof for releasing a metered dose of medicament under pressure, for example by operating a metered dose valve inside the canister body. The canister may be operable by pressing by hand on the main canister body.

In cases in which one or more support rails or inner wall support formations are provided, the canister may at all times when within the canister chamber have a clearance of about 0.25 to 0.35 mm from the first inner wall support formation. The clearance may be almost exactly 0.3 mm. This clearance which may apply to the canister body itself or to the canister once a label has been applied, is enough to allow smooth motion of the canister in the inhaler while at the same time preventing substantial rocking of the canister which could result in inaccurate counting by a dose counter of the inhaler, especially when lower face of the canister is arranged to engage an actuator member of the dose counter for counting purposes.

According to a further aspect of the invention, a method of assembling a dose counter for an inhaler comprises the steps of providing a tape with dosing indicia thereon; providing tape positioning indicia on the tape; and stowing the tape while monitoring for the tape positioning indicia with a sensor. The method advantageously permits efficient and accurate stowing of the tape, e.g. by winding.

The dosing indicia may be provided as numbers, the tape positioning indicia may be provided as one or more lines across the tape. The stowing step comprises winding the tape onto a bobbin or shaft, and, optionally, stopping winding when the positioning indicia are in a predetermined position. The tape may be provided with pixelated indicia at a position spaced along the tape from the positioning indicia. The tape may also be provided with a priming dot.

According to a further aspect of the invention, a tape system for a dose counter for an inhaler has a main elongate tape structure, and dosing indicia and tape positioning indicia located on the tape structure. The tape positioning indicia may comprise at least one line extending across the tape structure. The tape system may comprise pixelated indicia located on the tape structure and spaced from the positioning indicia. The tape system may comprise a priming dot located on the tape structure. The positioning indicia may be located between the timing dot and the pixelated indicia. The main elongate tape structure may have at least one end thereof wound on a bobbin or shaft.

A further aspect of the invention provides a method of designing an incremental dose counter for an inhaler comprising the steps of calculating nominal canister fire and dose counter positions for a dose counter actuator of the inhaler; calculating a failure/success rate for dose counters built to tolerance levels for counting each fire of inhalers in which the dose counter actuators may be applied; and selecting a tolerance level to result in said failure/success rate to be at or below/above a predetermined value. This is highly advantageous in that it allows an efficient and accurate prediction of the reliability of a series of inhaler counters made in accordance with the design.

The method of designing may include selecting the failure/success rate as a failure rate of no more than one in 50 million. The method of designing may include setting an average count position for dose counters built to the tolerances to be at or after an average fire position thereof during canister firing motion. The method of designing may include setting the average count position to be about 0.4 to 0.6 mm after the average fire position, such as about 0.48 mm after. The method of designing may include setting tolerances for the standard deviation of the fire position in dose counters built to the tolerances to be about 0.12 to 0.16 mm, such as about 0.141 mm. The method of designing may include setting tolerances for the standard deviation of the count positions in dose counters built to the tolerances to be about 0.07 to 0.09 mm, such as about 0.08 mm. A further aspect of the invention provides a computer implemented method of designing an incremental dose counter for an inhaler which includes the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing in a production run a series of incremental dose counters for inhalers which comprises manufacturing the series of dose counters in accordance with the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing a series of incremental dose counters for inhalers, which comprises manufacturing the dose counters with nominal canister fire and dose count positions of a dose counter actuator relative to a dose counter chassis (or inhaler main body), and which includes building the dose counters with the average dose count position in the series being, in canister fire process, at or after the average canister fire position in the series.

According to a further aspect of the invention, the method provides fitting each dose counter in the series of incremental dose counters to a corresponding main body of an inhaler.

These aspects advantageously provide for the production run of a series of inhalers and dose counters which count reliably in operation.

According to a further aspect of the invention, an incremental dose counter for a metered dose inhaler has a body arranged to retain a canister for movement of the canister relative thereto, the incremental dose counter having a main body, an actuator arranged to be driven and to drive an incremental output member in a count direction in response to canister motion, the actuator being configured to restrict motion of the output member in a direction opposite to the count direction. This advantageously enables an inhaler dose counter to keep a reliable count of remaining doses even if dropped or otherwise jolted.

The output member may comprise a ratchet wheel. The actuator may comprise a pawl and in which the ratchet wheel and pawl are arranged to permit only one-way ratcheting motion of the wheel relative to the pawl. The dose counter may include an anti-back drive member fixed to the main body. In a rest position of the dose counter, the ratchet wheel is capable of adopting a configuration in which a back surface of one tooth thereof engages the anti-back drive member and the pawl is spaced from an adjacent back

surface of another tooth of the ratchet wheel without positive drive/blocking engagement between the pawl and wheel.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention may be carried out in various ways and preferred embodiment of a dose counter, inhaler and methods of assembly, design and manufacture will now be described with reference to the accompanying drawings in which:

FIG. **1** is an isometric view of a main body of an embodiment of an inhaler related to the invention together with a mouthpiece cap therefor;

FIG. **2** is a top plan view of the components as shown in FIG. **1**;

FIG. **3**A is a section on the plane **3**A-**3**A in FIG. **2**;

FIG. **3**B is a view corresponding to FIG. **3**A but with a dose counter fitted to the main body of the inhaler;

FIG. **4**A is an exploded view of the inhaler main body, mouthpiece cap, dose counter and a dose counter window;

FIG. **4**B is a view in the direction **4**B in FIG. **4**C of a spring retainer of the dose counter;

FIG. **4**C is a top view of the spring retainer of FIG. **4**B;

FIG. **5** is a bottom view of the assembled inhaler main body, mouthpiece cap, dose counter and dose counter window;

FIGS. **6**A, **6**B, **6**C, **6**D, **6**E, **6**F, **6**G and **6**H are various views of dose counter components of the inhaler;

FIGS. **7**A and **7**B are sectional views showing canister clearance inside the main body of the inhaler;

FIG. **7**C is a further sectional view similar to that of FIG. **7**B but with the canister removed;

FIG. **7**D is a top plan view of the inhaler main body;

FIGS. **8**A, **8**B, **8**C and **8**D show the inhaler main body and dose counter components during assembly thereof;

FIG. **9** shows a sectional side view of a datum line for an actuator pawl of the dose counter;

FIGS. **10**A, **10**B, **10**C, **10**D, **10**E and **10**F show various side views of positions and configurations of the actuator pawl, a ratchet wheel, and a count pawl;

FIG. **11** shows distributions for tolerances of start, reset, fire, count and end positions for the actuator of the dose counter;

FIG. **12** is an enlarged version of part of FIG. **4**A;

FIG. **13** shows an end portion of a tape of the dose counter;

FIG. **14** shows a computer system for designing the dose counter;

FIG. **15** is an isometric view of a stock bobbin modified in accordance with the present invention for use in the dose counter of the inhaler of FIGS. **1** to **14**;

FIG. **16** shows an end view of the stock bobbin of FIG. **15**;

FIG. **17** is a section through a longitudinal axis of the stock bobbin of FIGS. **15** and **16**;

FIGS. **18**A, **18**B and **18**C are views of the stock bobbin of FIGS. **15** to **17** mounted in the dose counter chassis of FIGS. **1** to **14**, with the control elements of the forks of the second shaft (or split pin) having a profile slightly different to that in FIG. **6**F, with the forks in a compressed configuration;

FIGS. **19**A, **19**B and **19**C are views equivalent to FIGS. **18**A to **18**C but with the forks in a more expanded configuration due to a different rotational position of the stock bobbin;

FIG. **20** is an isometric view of the chassis assembled and including the stock bobbin of FIGS. **15** to **17** but excluding the tape for reasons of clarity;

FIG. **21** is a view of a preferred embodiment of a dry powder inhaler in accordance with the present invention;

FIG. **22** is an exploded view of the inhaler of FIG. **21**;

FIG. **23** is a view of a dose counter of the inhaler of FIG. **21**;

FIG. **24** is an exploded view of the dose counter shown in FIG. **23**;

FIG. **25** is an exploded view of parts of the inhaler of FIG. **21**; and

FIG. **26** is a view of a yoke of the inhaler of FIG. **21**.

DETAILED DESCRIPTION OF THE INVENTION

FIG. **1** shows a main body **10** of a manually operated metered dose inhaler **12** in accordance with an embodiment related to the present invention and having a mouthpiece cap **14** securable over a mouthpiece **16** of the main body.

The main body has a canister chamber **18** into which a canister **20** (FIG. **7**A) is slideable. The canister **20** has a generally cylindrical main side wall **24**, joined by a tapered section **26** to a head portion **28** having a substantially flat lower face **30** which has an outer annular drive surface **32** arranged to engage upon and drive an actuation pin **34** of a dose counter **36** as will be described. Extending centrally and axially from the lower face **30** is a valve stem **38** which is arranged to sealingly engage in a valve stem block **40** of the main body **10** of the inhaler **12**. The valve stem block **40** has a passageway **42** leading to a nozzle **44** for directing the contents of the canister **20**, namely active drug and propellant, towards an air outlet **46** of the inhaler main body **12**. It will be appreciated that due to gaps **48** between the canister **20** and an inner wall **50** of the main body **10** of the inhaler **12** an open top **52** of the main body **10** forms an air inlet into the inhaler **12** communicating via air passageway **54** with the air outlet **46**, such that canister contents exiting nozzle **44** mix with air being sucked by the user through the air passageway **54** in order to pass together through the air outlet and into the mouth of the user (not shown).

The dose counter **36** will now be described. The dose counter **36** includes an actuation pin **34** biased upwardly from underneath by a return spring **56** once installed in the main body **10**. As best shown in FIGS. **4**A, **6**H and **8**A, the pin **34** has side surfaces **58**, **60** arranged to slide between corresponding guide surfaces **62**, **64** located in a dose counter chamber **66** of the main body **10**, as well as an end stop surface **68** arranged to engage a corresponding end stop **70** formed in the dose counter chamber **66** to limit upward movement of the pin **34**. The pin **34** has a top part **72** which is circularly cylindrical and extends through an aperture **74** formed through a separator wall **76** which separates the canister chamber **18** from the dose counter chamber **66**. The top part **72** of the pin **34** has a flat top surface **78** which is arranged to engage the outer annular drive surface **32** of the canister **20**.

The actuation pin **34** is integrally formed with a drive or actuator pawl **80**. The actuator pawl **80** has a generally inverted U-shape configuration, having two mutually spaced and parallel arms **82**, **84** extending from a base portion of the actuation pin **34**, each holding at respective distal ends **88** thereof opposite ends of a pawl tooth member **90** which extends in a direction substantially perpendicular to the arms **82**, **84**, so as to provide what may be considered a "saddle" drive for pulling on each of the 11 drive teeth **92** of a ratchet wheel **94** of an incremental drive system **96** or ratchet mechanism **96** of the dose counter **36**. As shown for example in FIG. **10**B, the pawl tooth member **90** has a sharp lower

longitudinal side edge **98** arranged to engage the drive teeth **92**, the edge-to-surface contact provided by this engagement providing very accurate positioning of the actuator pawl **80** and resultant rotational positioning of the ratchet wheel **94**.

The dose counter **36** also has a chassis preassembly **100** which, as shown in FIGS. **4**A and **6**A, includes a chassis **102** having a first shaft **104** receiving the ratchet wheel **94** which is secured to a tape reel shaft **106**, and a second shaft (or split pin) **108** which is parallel to and spaced from the first shaft **104** and which slidably and rotationally receives a tape stock bobbin **110**.

As shown in FIG. **6**B, when the inhaler has not been used at all, the majority of a tape **112** is wound on the tape stock bobbin **110** and the tape **112** has a series of regularly spaced numbers **114** displayed therealong to indicate a number of remaining doses in the canister **20**. As the inhaler is repeatedly used, the ratchet wheel **94** is rotated by the actuator pawl **80** due to operation of the actuation pin **34** by the canister **20** and the tape **112** is incrementally and gradually wound on to the tape reel shaft **106** from the second shaft **108**. The tape **112** passes around a tape guide **116** of the chassis **102** enabling the numbers **114** to be displayed via a window **118** in a dose counter chamber cover **120** having a dose marker **132** formed or otherwise located thereon.

As shown in FIGS. **6**A and **6**D, the second shaft **108** is forked with two forks **124**, **126**. The forks **124**, **126** are biased away from one another. The forks have located thereon at diametrically opposed positions on the second shaft **108** friction or control elements **128**, **130**, one on each fork. Each control element extends longitudinally along its respective fork **124**, **126** and has a longitudinally extending friction surface **132**, **134** which extends substantially parallel to a longitudinal axis of the second shaft and is adapted to engage inside a substantially cylindrical bore **136** inside the tape stock bobbin **110**. This control arrangement provided between the bore **136** and the control elements **128**, **130** provides good rotational control for the tape stock bobbin **110** such that it does not unwind undesirably such as when the inhaler is dropped. The tape force required to unwind the tape stock bobbin **110** and overcome this friction force is approximately 0.1 N.

As can be seen in FIG. **6**D, as well as FIGS. **6**G and **10**A to **10**F, the chassis **102** is provided with an anti-back drive tooth **138** or count pawl **138** which is resiliently and substantially fixedly mounted thereto. As will be described below and as can be seen in FIGS. **10**A to **10**F, when the actuation pin **34** is depressed fully so as to fire the metered valve (not shown) inside the canister **20**, the actuator pawl **80** pulls down on one of the teeth **92** of the ratchet wheel **94** and rotates the wheel **94** anticlockwise as shown in FIG. **6**D so as to jump one tooth **92** past the count pawl **138**, thereby winding the tape **112** a distance incrementally relative to the dose marker **122** on the dose counter chamber **120** so as to indicate that one dose has been used.

With reference to FIG. **10**B, the teeth of the ratchet wheel **94** have tips **143** which are radiused with a 0.1 mm radius between the flat surfaces **140**, **142**. The ratchet wheel **94** has a central axis **145** which is 0.11 mm above datum plane **220** (FIG. **9**). A top/nose surface **147** of the anti-back drive tooth **138** is located 0.36 mm above the datum plane **220**. The distance vertically (i.e. transverse to datum plane **220**—FIG. **9**) between the top nose surface **147** of the anti-back drive tooth is 0.25 mm from the central axis **145** of the wheel **94**. Bump surface **144** has a lateral extent of 0.20 mm, with a vertical length of a flat **145'** thereof being 1 mm, the width of the bump surface being 1.22 mm (in the direction of the axis **145**), the top **149** of the bump surface **144** being 3.02 mm vertically below the axis **145**, and the flat **145'** being spaced a distance sideways (i.e. parallel to the datum plane **220**) 2.48 mm from the axis **145**. The top surface **78** of the pin **34** (FIG. **6**H) is 11.20 mm above the datum plane **220** (FIG. **9**) when the actuator pawl **80** and pin **34** are in the start configuration. The length of the valve stem **22** is 11.39 mm and the drive surface **32** of the canister **20** is 11.39 mm above the datum plane **220** when the canister is at rest waiting to be actuated, such that there is a clearance of 0.19 mm between the canister **20** and the pin **34** in this configuration.

FIGS. **10**A and **10**B show the actuator pawl **80** and ratchet wheel **94** and count pawl **138** in a start position in which the flat top **78** of the pin **34** has not yet been engaged by the outer annular drive surface **32** of the canister **20** or at least has not been pushed down during a canister depression.

In this "start" position, the count pawl **138** engages on a non-return back surface **140** of one of the teeth **92** of the ratchet wheel **94**. The lower side edge **98** of the actuator pawl is a distance "D" (FIG. **9**) 1.33 mm above datum plane **220** which passes through bottom surface or shoulder **41** of valve stem block **40**, the datum plane **220** being perpendicular to a main axis "X" of the main body **10** of the inhaler **12** which is coaxial with the centre of the valve stem block bore **43** and parallel to a direction of sliding of the canister **20** in the main body **10** of the inhaler **12** when the canister is fired.

As shown in FIG. **10**B, an advantageous feature of the construction is that the pawl tooth/actuator **90** acts as a supplementary anti-back drive member when the inhaler **12** is not being used for inhalation. In particular, if the inhaler **12** is accidentally dropped, resulting in a jolt to the dose counter **36** then, if the wheel **94** would try to rotate clockwise (backwards) as shown in FIG. **10**B, the back surface **140** of a tooth will engage and be blocked by the tooth member **90** of the pawl **80**. Therefore, even if the anti-back drive tooth **138** is temporarily bent or overcome by such a jolt, undesirable backwards rotation of the wheel **94** is prevented and, upon the next canister firing sequence, the pawl **90** will force the wheel **94** to catch up to its correct position so that the dose counter **36** continues to provide correct dosage indication.

FIG. **10**C shows a configuration in which the actuator pawl **80** has been depressed with the pin **34** by the canister **20** to a position in which the side edge **98** of the pawl tooth member **90** is just engaged with one of the teeth **92** and will therefore upon any further depression of the pin **34** begin to rotate the wheel **94**. This is referred to as a "Reset" position or configuration. In this configuration, the lower side edge **98** of the actuator **80** is 0.64 mm above the datum plane **220**.

FIG. **10**D shows a configuration in which the actuator pawl **80** has been moved to a position lower than that shown in FIG. **10**C and in which the metered dose valve (not shown) inside the canister has at this very position fired in order to eject active drug and propellant through the nozzle **44**. It will be noted that in this configuration the count pawl **138** is very slightly spaced from the back surface **140** of the same tooth **92** that it was engaging in the configuration of FIG. **10**D. The configuration shown in FIG. **10**D is known as a "Fire" configuration. In this configuration the lower side edge **98** of the actuator **80** is 0.47 mm below the datum plane **220**.

FIG. **10**E shows a further step in the sequence, called a "Count" position in which the actuator pawl **80** has rotated the ratchet wheel **94** by the distance circumferentially angularly between two of the teeth **92**, such that the count pawl **138** has just finished riding along a forward surface **142** of one of the teeth **92** and has resiliently jumped over the tooth

into engagement with the back surface **140** of the next tooth. Accordingly, in this "Count" configuration, a sufficiently long stroke movement of the pin **34** has occurred that the tape **112** of the dose counter **36** will just have counted down one dose. In this configuration, the lower side edge **98** of the actuator is 0.95 mm below the datum plane **220**. Accordingly, in this position, the actuator **80** generally, including edge **98**, is 0.48 mm lower than in the fire configuration. It has been found that, although the count configuration happens further on than the fire configuration, counting is highly reliable, with less than 50 failed counts per million. This is at least partially due to momentum effects and to the canister releasing some back pressure on the user in some embodiments as its internal metering valve fires.

In the configuration of FIG. **10**F, the pawl **80** has been further depressed with the pin **34** by the canister **20** to a position in which it is just disengaging from one of the teeth **92** and the actuator pawl **80** is assisted in this disengagement by engagement of one of the arms **84** with a bump surface **144** on the chassis **102** (see FIG. 6G) and it will be seen at this point of disengagement, which is called an "End" configuration, the count pawl **138** is positioned exactly halfway or substantially halfway between two of the drive teeth **92**. This advantageously means therefore that there is a minimum chance of any double counting or non-counting, which would be undesirable. In the end configuration, the side edge **98** of the actuator is 1.65 mm below the datum plane **220**. It will be appreciated that any further depression of the actuator pawl **80** and pin **34** past the "End" configuration shown in FIG. **10**F will have no effect on the position of the tape **112** displayed by the dose counter **36** since the actuator pawl **80** is disengaged from the ratchet wheel **94** when it is below the position shown in FIG. **10**F.

As shown in FIGS. 7C and 7D, the inner wall **50** of the main body **10** is provided with a two-step support rail **144** which extends longitudinally along inside the main body and is located directly adjacent the aperture **74**. As shown in FIG. 7B a diametrically opposed two-step support rail **146** is also provided and this diametrically opposed in the sense that a vertical plane (not shown) can pass substantially directly through the first rail **144**, the aperture **74**, a central aperture **148** of the valve stem block **40** (in which canister stem **25** is located) and the second two-step support rail **146**. As shown in FIG. 7A and schematically in FIG. 7B, the rails **144, 146** provide a maximum clearance between the canister **20** and the rails **144, 146** in a radial direction of almost exactly 0.3 mm, about 0.25 to 0.35 mm being a typical range. This clearance in this plane means that the canister **20** can only rock backwards and forwards in this plane towards away from the actuation pin **34**. A relatively small distance and this therefore prevents the canister wobbling and changing the height of the actuation pin **34** a as to undesirably alter the accuracy of the dose counter **36**. This is therefore highly advantageous.

The inner wall **50** of the main body **10** is provided with two further two-step rails **150** as well as two pairs **152, 154** of rails extending different constant radial amounts inwardly from the inner wall **50**, so as to generally achieve a maximum clearance of almost exactly 0.3 mm around the canister **20** for all of the rails **144, 146, 150, 152, 154** spaced around the periphery of the inner wall **50**, in order to prevent undue rocking while still allowing canister motion freely inside the inhaler **12**. It will be clear from FIG. 7C for example that the two-step rails have a first portion near an outlet end **156** of the canister chamber **18**, the first portion having a substantially constant radial or inwardly-extending width, a first step **160** leading to a second portion **162** of the rail, the second portion **102** having a lesser radial or inwardly extending extent than the first portion **156**, and finally a second step **164** at which the rail merges into the main inner wall **50** main surface.

A method of assembling the inhaler **12** will now be described.

With reference to FIG. 8A, the main body **10** of the inhaler **12** is formed by two or more plastics mouldings which have been joined together to the configuration shown.

As shown in FIG. 8B, the actuator pawl **80** and pin **34** are translated forward into position into a pin receiving area **166** in the dose counter chamber **66** and the pin **34** and actuator **80** may then be raised until the pin **34** emerges through the aperture **74**.

Next, the return spring **56** may be inserted below the pin **34** and a generally cylindrical annular lower end **168** of the spring **56** may be moved by a tweezer or tweezer-like assembly tool (not shown) into engagement with a shelf **170** of a spring retainer **172** in the dose counter chamber **66**. The spring retainer **172** is U-shaped and the shelf **170** is U-shaped and has a recess **174** formed below it. As shown in FIGS. 4B, 4C and **12** shelf **170** includes three chamfer surfaces **176, 178, 180** arranged to assist in moving the lower end of the spring **168** into position onto the shelf using the assembly tool (not shown). Once the lower end of the spring **168** is in place, the assembly tool (not shown) can easily be removed at least partly via the recess **174** below the lower end **168** of the spring **56**.

The tape **112** is attached at one end (not shown) to the tape stock bobbin **110** and is wound onto the bobbin by a motor **200** (FIG. 13) having a hexagonal output shaft **202** which engages in a hexagonal socket **204** (FIG. 6B) of the bobbin. During winding, the tape is monitored by a sensor **206**, which may be in the form of a camera or laser scanner, which feeds data to a computer controller **205** for the motor **200**. The controller **205** recognises three positioning markers **210** in the form of lines across the tape **112** and stops the motor **202** when the tape **112** is nearly fully wound onto the bobbin **110**, such that the distal end **212** of the tape **112** can be secured, e.g. by adhesive, to the tape reel shaft **106**. The controller **205** also recognises a pixelated tape size marker **214** observed by the sensor **206** and logs in a stocking system data store **217** details of the tape **112** such as the number of numbers **114** on the tape, such as one hundred and twenty or two hundred numbers **114**. Next, the tape reel shaft is wound until an appropriate position of the lines **210** at which a priming dot **216** will, once the bobbin **110** and reel shaft **106** are slid onto the second shaft **108** and second shaft **104**, be in a position to be located in the window **118** when the inhaler **12** is fully assembled. In the embodiments, the bobbin **110** and reel shaft **106** may be slid onto the shafts **108, 104** before the tape **112** is secured to the reel shaft **106** and the reel shaft may then be wound to position the priming dot **216**.

Next, the assembled dose counter components of the chassis preassembly **100** shown in FIG. **6**B may as shown in FIG. **8**C be inserted into the dose counter chamber **66**, with pins **182, 184, 186** formed on the main body **10** in the dose counter chamber **66** passing through apertures or slots **188, 190, 192** formed on the chassis **102**, such that the pins **182, 184, 186** extend through (or at least into) the apertures or slots **188, 190, 192**. With the chassis **102** being relatively firmly pushed towards the main body **10**, the pins **182, 184, 186** are then heat staked and the chassis **102** is therefore after this held very firmly in position in the main body and is unable to move, thereby assisting in providing great accuracy for the dose counter **36**. Next, as shown in FIG. **8**D, the

dose counter chamber cover **120** may be fitted over the dose counter chamber **66** and may be secured in place such as by welding, with the priming dot **216** being displayed through the window.

The user can, when readying the inhaler **12** for first use, prime the inhaler by depressing the canister **20** three times which will bring the first number **114** on the tape into display through the window **118** in place of the priming dot **216**, the number **114** shown in FIG. **8**D being "200", thereby indicating that 200 doses are remaining to be dispensed from the canister **20** and inhaler **12**.

As shown in FIG. **8**D, and in FIG. **5**, an open drain hole **194** is provided at the bottom of the dose counter chamber **66** by a substantially semi-circular cut-out or recess formation **196** in a lower surface **198** of the main body **10** of the inhaler. Accordingly, if the user (not shown) should decide to wash the main body **10** of the inhaler, for example after encountering an unhygienic situation or simply as a matter of choice, the drain hole **194** allows initial draining of water from inside the dose counter chamber **66** and also thereafter evaporation of water or any aqueous matter in the dose counter chamber **66** so that the window **118** does not mist up undesirably.

FIG. **14** shows a computer system **230** for designing the dose counter **36** and in particular for calculating distributions representative of average positions and standard deviations in a production series of inhalers of the start, reset, fire, count and end positions of the actuator lower side edge **98** relative to the datum plane **220** (FIG. **9**) and therefore of the actuator pawl **80** generally relative to the ratchet wheel **94**, chassis **102** and, when the inhaler **12** is fully assembled, the main body **10** of the inhaler **12**. The computer system **230** includes a data store **232**, a CPU **234**, an input device **236** (such as a keyboard or communication port) and an output device **238** (such as a communications port, display screen and/or printer). A user may enter data via the input device **236** which may be used by the CPU **234** in a mathematical calculation to predict count failure rates when the various dose counters are to be built in a series with dose counter positions set with given averages and standard deviations and taking into account any momentum/inertia effects and metering valve user-back-pressure reduction effect which will occur upon canister firing of a given type of canister. The computer system **230** is thus mathematically used to design the distributions. For the inhaler **12** described herein with the dose counter **36** and canister **20**, the distributions are designed as shown in FIG. **11**. The x axis shows distance of the lower side surface **98** of the actuator **80** above the datum plane **220** and the y axis is representative of the distribution. Thus, curve **240** shows that the start configuration has an average 1.33 mm above the datum plane **200** (standard deviation is 0.1 mm), curve **242** shows that the reset configuration has an average of 0.64 mm above the datum plane **220** (standard deviation is 0.082 mm), curve **244** shows the fire configuration has an average 0.47 mm below the datum plane **220** (standard deviation is 0.141 mm), curve **246** shows the count configuration has an average 0.95 mm below the datum plane **220** (standard deviation is 0.080 mm), and curve **248** shows the end configuration has an average of 1.65 mm below the datum plane **220** (standard deviation is 0.144 mm).

FIGS. **15** to **20** show a version of the inhaler modified in accordance with the present invention. In these drawings, the same reference numerals have been used to those in the earlier drawings to denote the equivalent components. The inhaler **12** is the same as that in FIGS. **1** to **14** apart from the following modifications.

First, it can be seen that there is a modification in that the drive teeth **92** of the ratchet wheel **94** have a different profile to that in FIGS. **1** to **14**. There are also only nine ratchet teeth **94** in this embodiment instead of eleven.

Additionally, as shown in FIGS. **18**C and **19**C, the control elements **128**, **130** on the forks **124**, **126** of the second shaft **108** have a tapered profile which is different to the profile of the control elements **128**, **130** shown in FIG. **6**F. Either profile can be used in the embodiment of FIGS. **15** to **20** however.

Furthermore, as shown in FIG. **15**, the tape stock bobbin **110** has an inwardly facing generally cylindrical engagement surface **300** with a wavelike form extending partially therealong. The engagement surface **300** has a cross-section **301** perpendicular to the longitudinal length of the stock bobbin **110** which is constant therealong. This cross-section **301** can be seen in FIG. **16** and consists of a series of ten regularly spaced concavities **302** and ten convex wall portions **304**. The convex wall portions **304** are equi-spaced between the concavities **302**. Each concavity **302** has a radius of 0.2 mm. Each convex wall portion **304** also has a radius of 0.2 mm. Finally, the cross section **301** also includes flat wall portions **306** between all of the radiused wall portions of the concavities **302** and convex wall portions **304**. The geometry of the cross-section **301** is therefore defined by the radii of the concavities **302** and convex wall portions **304**, the flat wall portions **306** and the fact that there are ten concavities **302** and convex wall portions **304**.

The minor diameter of the engagement surface **300**, i.e. between the tips of opposite convex wall portions **304**, is 2.46 mm. The major diameter of the engagement surface **300**, i.e. between the outermost portions of the concavities **302**, is 2.70 mm. The undeformed tip to tip maximum diameter of the forks **124**, **126** of the split pin (the second shaft) **108**, i.e. in the region of the maximum radio extent of the control elements **128**, **130**, is 3.1 millimetres and it will therefore be appreciated that the forks **124**, **126** are resiliently compressed once the stock bobbin **110** has been assembled onto the split pin **108** in all rotational configurations of the stock bobbin **110** relative to the split pin **108**. The minimum gap between the forks **124**, **126** in the plane of the cross sections of FIGS. **18**C and **19**C is 1 mm when the split pin **108** is in the undeformed, pre-inserted state. When the split pin **108** is at maximum compression, as shown in FIGS. **18**A to **18**C when the control elements **128**, **130** are shown to be engaged on top of the convex wall portions **304**, the gap **308** between the tips **310**, **312** of the forks **124**, **126** is 0.36 mm. On the other hand, when the split pin **108** is at minimum compression (once inserted into the stock bobbin) as shown in FIGS. **19**A to **19**C, when the control elements **128**, **130** rest in the concavities **302**, the gap between the tips **310**, **312** of the forks **124**, **126** is 0.6 mm. The control elements **128**, **130** are outwardly radiused with a radius also of 0.2 mm such that they can just rest on the concavities **302** with full surface contact (at least at an axial location on the split pin where the tapered control elements are at their maximum radial extent), without rattling in, locking onto or failing to fit in the concavities **302**. The radii of the control elements **128**, **130** is therefore preferably substantially the same as the radii of the concavities **302**

It will be appreciated that whereas FIGS. **18**B and **19**B are end views along the coaxial axis of the stock bobbin **110** and split pin **108**, FIGS. **18**A and **19**A are cross-sections. FIG. **19**A is a section on the plane A-A' in FIG. **19**C and FIG. **18**A is a section at the same plane, but of course with the stock bobbin **110** rotated relative to the split pin **108**.

As the inhaler **12** is used and the ratchet wheel **94** rotates in order to count used doses, the stock bobbin rotates incrementally through rotational positions in which rotation is resisted, i.e. due to increasing compression of the split pin **108** at such rotational positions, and rotational positions in which rotation is promoted, i.e. due to decreasing compression of the split pin **108** at such rotational positions and this may involve a click forward of the stock bobbin **110** to the next position equivalent to that in FIGS. **19**A to **19**C in which the control elements **128**, **130** of the split pin art located in the concavities **302**. This functionality firstly allows the stock bobbin to unwind during use as required, but also prevents the tape **112** from loosening during transit if the inhaler **12** is dropped, such as onto a hard surface. This is highly advantageous, since the tape **11** is prevented from moving to a position in which it will give an incorrect reading regarding the number of doses in the canister.

During compression and expansion of the forks in the radial direction between the two configurations shown in FIGS. **18**C and **19**C, the forks **124**, **126** rotate about a point **316** on the split pin where the forks **124**, **126** come together. This rotational action means that there is a camming action between the forks **124**, **126** and the engagement surface **300** without significant friction but, nevertheless, the resilient forces provided by the regulator formed by the engagement surface **300** and forks **124**, **126** are able to regulate unwinding of the tape such that it does not easily occur during transit or if the inhaler **12** is dropped. It has been found during testing that a force of 0.3 to 0.4 N needs to be applied to the tape **112** to overcome the regulator at the stock bobbin **110**. 0.32 N is achieved with the control elements **128** having the profile shown in FIG. **19**C and 0.38 N is achieved with the profile of the control elements **128** altered to be as shown as described with reference to FIG. **6**F. These forces are substantially higher than the 0.1 N force mentioned above and undesirable movement of the tape is substantially avoided even if the inhaler is dropped onto a hard surface. The modified arrangement of FIGS. **15** to **20** does not provide this force "constantly" such that there is overall not an undesirably high friction of the tape **112** as it passes over the other components of the dose counter because, due to the incremental nature of the resilient forces at the regulator, the tape **112** can incrementally relax as it slides over the stationary chassis components.

Instead of having ten concavities **302** and convex wall portions **304**, other numbers may be used, such as 8 or 12. However, it is preferred to have an even number, especially since two control elements **128**, **130** are provided, so that all of the control elements **128**, **130** will expand and contract simultaneously. However, other arrangements are envisaged with 3 or more forks and the number of concavities/convex wall portions may be maintained as an integer divisible by the number of forks to maintain a system with simultaneous expansion/contraction. For example, the use of 9, 12 or 15 concavities/convex wall portions with 3 forks is envisaged.

Instead of having the engagement surface **300** on the inside of the stock bobbin **110**, it could be placed on the outside of the stock bobbin **110** so as to be engaged by flexible external legs/pawls or similar.

It will be noted that the regulator provided by the engagement surface **300** and forks **124**, **126** does not only allow rotation of the stock bobbin in one direction as is the case with the ratchet wheel **94**. Rotation in both directions is possible, i.e. forwards and backwards. This means that during assembly, the stock bobbin **110** can be wound backwards during or after fitting the bobbin **100**, shaft **106** and tape **112** onto the carriage **102**, if desired.

The stock bobbin **110** and the carriage **102** including the split pin **108** are both moulded of polypropylene material.

It will be seen from FIG. **16** that the cross-sectional shape **301** is not symmetrical within the hexagonal socket **204**. This has enabled the hexagonal socket **204** to be maintained at a useful size while still allowing the desired size and geometry of the cross section **301** to fit without interfering with the hexagonal shape of the hexagonal socket **204** and also permits moulding to work during manufacture.

As shown in FIG. **17**, the stock bobbin **110** has a series of four circumferential ribs **330** inside it and a spaced thereabout. These hold the stock bobbin **110** on the correct side of the mould tool during moulding.

FIGS. **21** and **22** show a preferred embodiment in accordance with the invention of an inhaler **510** for dispensing a dry-powdered medicament in metered doses for patient inhalation. The inhaler **510** is as disclosed in FIGS. **1** to **16** or EP-A-1330280, the contents of which are hereby fully incorporated herein by reference, but with the stock bobbin **110** and second shaft **108** of the dose counter **516** modified so as to be as in FIGS. **15** to **20** hereof. Thus, the dry powder inhaler **510** generally includes a housing **518**, and an assembly **512** received in the housing (see FIG. **21**). The housing **518** includes a case **520** having an open end **522** and a mouthpiece **524** (FIG. **25**) for patient inhalation, a cap **526** secured to and closing the open end **522** of the case **520**, and a cover **528** pivotally mounted to the case **520** for covering the mouthpiece **524**. As shown in FIG. **22**, the inhaler **510** also includes an actuation spring **569**, first yoke **566** with opening **572**, bellows **540** with crown **574**, a reservoir **514**, second yoke **568** with hopper **542** and dose counter **516** mounted thereto, and case **520** has transparent window **5130** thereon for viewing dose counter tape indicia **5128**. The dose metering system also includes two cams **570** mounted on the mouthpiece cover **528** and movable with the cover **528** between open and closed positions. The cams **570** each include an opening **580** for allowing outwardly extending hinges **582** of the case **520** to pass therethrough and be received in first recesses **584** of the cover **528**. The cams **570** also include bosses **586** extending outwardly and received in second recesses **588** of the cover **528**, such that the cover **528** pivots about the hinges **582** and the cams **570** move with the cover **528** about the hinges **582**. As described in EP-A-1330280, cams **570** act upon cam followers **578** to move second yoke **568** up and down and thereby operate dose counter by engagement of pawl **5138** on the second yoke **568** with teeth **5136**. Remaining components of the inhaler are provided as, and operate as described, in EP-A-1330280.

The dose counting system **516** therefore includes a ribbon or tape **5128** (FIGS. **23** & **24**), having successive numbers or other suitable indicia printed thereon, in alignment with a transparent window **5130** provided in the housing **18** (see FIG. **22**). The dose counting system **516** includes the rotatable stock bobbin **110** (as described above), an indexing spool **5134** rotatable in a single direction, and the ribbon **5128** rolled and received on the bobbin **110** and having a first end **5127** secured to the spool **5134**, wherein the ribbon **5128** unrolls from the bobbin **110** so that the indicia are successively displayed as the spool **5134** is rotated or advanced. In FIGS. **23** and **24** the wavelike engagement surface **300** of the bobbin **110** is not shown for the purposes of clarity.

The spool **134** is arranged to rotate upon movement of the yokes **566**, **568** to effect delivery of a dose of medicament from reservoir **514**, such that the number on the ribbon **5128** is advanced to indicate that another dose has been dispensed by the inhaler **510**. The ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase or

decrease upon rotation of the spool **5134**. For example, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, decrease upon rotation of the spool **5134** to indicate the number of doses remaining in the inhaler **510**. Alternatively, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase upon rotation of the spool **5134** to indicate the number of doses dispensed by the inhaler **10**.

The indexing spool **5134** includes radially extending teeth **5136**, which are engaged by pawl **5138** extending from a cam follower **578** of the second yoke **568** upon movement of the yoke to rotate, or advance, the indexing spool **5134**. More particularly, the pawl **5138** is shaped and arranged such that it engages the teeth **5136** and advances the indexing spool **5134** only upon the mouthpiece cover **528** being closed and the yokes **566**, **568** moved back towards the cap **526** of the housing **518**.

The dose counting system **516** also includes a chassis **5140** that secures the dose counting system to the hopper **542** and includes shafts **108**, **5144** for receiving the bobbin **110** and the indexing spool **5134**. As described above with reference to FIGS. **1** to **20**, the bobbin shaft **108** is forked and includes radially nubs **5146** for creating a resilient resistance to rotation of the bobbin **110** on the shaft **108** by engaging with the wavelike engagement surface **300** inside the bobbin **110**. A clutch spring **5148** is received on the end of the indexing spool **5134** and locked to the chassis **5140** to allow rotation of the spool **5134** in only a single direction.

Various modifications may be made to the embodiment shown without departing from the scope of the invention as defined by the accompanying claims as interpreted under patent law.

What is claimed is:

1. A dose counter for an inhaler, the dose counter having a counter display arranged to indicate dosage information, a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

2. The dose counter as claimed in claim **1** in which the counter display comprises a tape.

3. The dose counter as claimed in claim **2** in which the tape has dose counter indicia displayed thereon.

4. The dose counter as claimed in claim **2** wherein the first station comprises a first shaft, the tape being arranged on the first shaft and to unwind therefrom upon movement of the counter display.

5. The dose counter as claimed in claim **4** in which the first shaft is mounted for rotation relative to a substantially rotationally fixed element of the dose counter.

6. The dose counter as claimed in claim **5** in which the regulator comprises at least one projection on one of the first shaft and the substantially rotationally fixed element, which is arranged to engage incrementally with one or more formations on the other of the substantially rotationally fixed element and the first shaft.

7. The dose counter as claimed in claim **6** in which at least two said projections are provided.

8. The dose counter as claimed in claim **6** in which exactly two said projections are provided.

9. The dose counter as claimed in claim **6** in which each projection comprises a radiused surface.

10. The dose counter as claimed in claim **6** in which the at least one projection is located on the substantially rotationally fixed element which comprises a fixed shaft which is fixed to the main body of the dose counter, the first shaft being rotationally mounted to the fixed shaft.

11. The dose counter as claimed in claim **10** in which the fixed shaft has at least two flexible legs, and each leg has at least one said projection formed in an outwardly facing direction thereon, said one or more formations being formed on an inwardly facing engagement surface of the first shaft, said at least one projection being arranged to resiliently engage said one or more formations.

12. The dose counter as claimed in claim **10** in which the fixed shaft comprises a split pin with fork legs and in which each projection is located on a said fork leg.

13. The dose counter as claimed in claim **6** in which a series of said formations are provided.

14. The dose counter as claimed in claim **6** in which an even number of said formations is provided.

15. The dose counter as claimed in claim **6** in which from eight to twelve of said formations are provided.

16. The dose counter as claimed in claim **15** in which ten of said formations are provided.

17. The dose counter as claimed in claim **6** in which each said formation comprises a concavity formed on an engagement surface.

18. The dose counter as claimed in claim **17** in which each concavity comprises a radiused surface wall portion which merges on at least one side thereof into a flat wall portion surface.

19. The dose counter as claimed in claim **18** in which the engagement surface includes a series of said concavities and in which convex wall portions of the engagement surface are formed between each adjacent two said concavities, each said convex wall portion comprising a convex radiused wall portion.

20. The dose counter as claimed in claim **19** in which each convex radiused wall portion of each convex wall portion is connected by said flat wall portion surfaces to each concavity which is adjacent thereto.

21. The dose counter as claimed in claim **4** in which the first shaft comprises a substantially hollow bobbin.

22. The dose counter as claimed in claim **21** in which said one or more formations are located on an inner surface of the bobbin.

23. The dose counter as claimed in claim **4** wherein the drive system comprises a tooth ratchet wheel arranged to act upon a second shaft which is located at the second station, the second shaft being rotatable to wind the tape onto the second shaft.

24. The dose counter as claimed in claim **23** in which the second shaft is located on the main body of the dose counter spaced from and parallel to the first shaft.

25. The dose counter as claimed in claim **23** in which the tooth ratchet wheel is fixed to the second shaft and is arranged to rotate therewith.

26. The dose counter as claimed in claim **23** which includes an anti-back drive system which is arranged to restrict motion of the second shaft in a tape winding direction.

27. The dose counter as claimed in claim **1** in which the regulator provides a resistance force of greater than 0.1 N against movement of the counter display.

28. The dose counter as claimed in claim **27** in which the resistance force is greater than 0.3 N.

29. The dose counter as claimed in claim **27** in which the resistance force is from 0.3 to 0.4 N.

* * * * *

EXHIBIT 4

8473763

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 9, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: *11,395,889*
ISSUE DATE: *July 26, 2022*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

Paula Smith
Certifying Officer


US011395889B2

(12) **United States Patent**
Walsh et al.

(10) **Patent No.: US 11,395,889 B2**
(45) **Date of Patent: Jul. 26, 2022**

(54) **DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR**

(71) Applicants: **Ivax Pharmaceuticals Ireland**, Waterford (IE); **Norton (Waterford) Limited**, Waterford (IE); **Teva Pharmaceuticals Ireland**, Waterford (IE)

(72) Inventors: **Declan Walsh**, County Kilkenny (IE); **Derek Fenlon**, County Wexford (IE); **Simon Kaar**, County Cork (IE); **Jan Geert Hazenberg**, County Kilkenny (IE); **Daniel Buck**, County Waterford (IE); **Paul Clancy**, Waterford (IE); **Robert Charles Uschold**, Leominster, MA (US); **Jeffrey A. Karg**, Hopkinton, MA (US)

(73) Assignees: **Ivax Pharmaceuticals Ireland**, Waterford (IE); **Norton (Waterford) Limited**, Waterford (IE); **Teva Pharmaceuticals Ireland**, Waterford (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/915,558**

(22) Filed: **Jun. 29, 2020**

(65) **Prior Publication Data**

US 2021/0016026 A1 Jan. 21, 2021

Related U.S. Application Data

(60) Continuation of application No. 15/804,735, filed on Nov. 6, 2017, now Pat. No. 10,695,512, which is a continuation of application No. 15/269,249, filed on Sep. 19, 2016, now Pat. No. 9,808,587, which is a continuation of application No. 14/103,324, filed on Dec. 11, 2013, now Pat. No. 9,463,289, which is a division of application No. 13/110,532, filed on May 18, 2011, now Pat. No. 8,978,966.

(Continued)

(51) **Int. Cl.**
A61M 15/00 (2006.01)
G06M 1/24 (2006.01)
A61M 11/00 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 15/0078*** (2014.02); ***A61M 11/00*** (2013.01); ***A61M 15/007*** (2014.02);
(Continued)

(58) **Field of Classification Search**
CPC A61M 15/0078; A61M 15/0025; A61M 15/0026; A61M 15/007; A61M 15/0071;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,174,890 A 11/1979 Johnson
4,669,838 A 6/1987 Hibbard
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2501726 9/2006
CN 1265601 9/2000
(Continued)

OTHER PUBLICATIONS

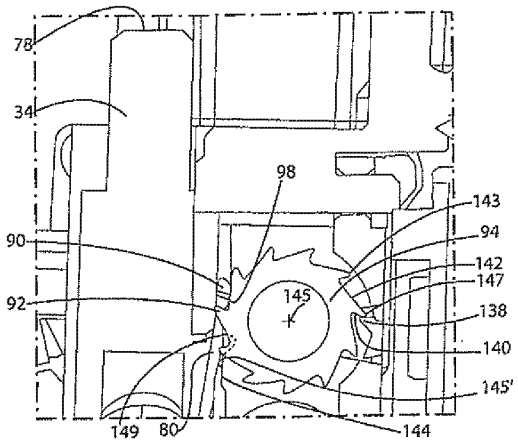
Advisory Action dated Mar. 13, 2017 for U.S. Appl. No. 14/699,567.
(Continued)

Primary Examiner — Daniel A Hess
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

An inhaler includes a main body having a canister housing, a medicament canister retained in a central outlet port of the canister housing, and a dose counter having an actuation member for operation by movement of the medicament canister. The canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall. The canister housing

(Continued)



has a longitudinal axis X which passes through the center of the central outlet port. The first inner wall canister support formation, the actuation member, and the central outlet port lie in a common plane coincident with the longitudinal axis X such that the first inner wall canister support formation protects against unwanted actuation of the dose counter by reducing rocking of the medicament canister relative to the main body of the inhaler.

6 Claims, 17 Drawing Sheets

Related U.S. Application Data

(60) Provisional application No. 61/417,659, filed on Nov. 29, 2010, provisional application No. 61/345,763, filed on May 18, 2010.

(52) **U.S. Cl.**
CPC ***A61M 15/009*** (2013.01); ***A61M 15/0025*** (2014.02); ***A61M 15/0026*** (2014.02); ***A61M 15/0065*** (2013.01); ***A61M 15/0071*** (2014.02); ***G06M 1/246*** (2013.01); *A61M 2202/064* (2013.01); *A61M 2205/6063* (2013.01); *A61M 2207/00* (2013.01); *A61M 2207/10* (2013.01); *Y10T 29/49* (2015.01); *Y10T 29/49764* (2015.01); *Y10T 29/49826* (2015.01)

(58) **Field of Classification Search**
CPC A61M 11/00; A61M 15/0065; A61M 15/009; G06M 1/246
USPC 128/203.12
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,687,359	A	8/1987	Barrus	
5,349,945	A	9/1994	Wass et al.	
5,482,030	A	1/1996	Klein	
5,861,911	A	1/1999	Oosaka	
6,142,339	A	11/2000	Blacker et al.	
6,446,627	B1 *	9/2002	Bowman	A61M 15/009 128/200.23
6,659,307	B1	12/2003	Stradella	
6,718,972	B2	4/2004	OLeary	
6,907,876	B1	6/2005	Clark et al.	
7,107,986	B2	9/2006	Rand et al.	
7,156,258	B2	1/2007	Eckert	
7,587,988	B2	9/2009	Bowman et al.	
7,661,423	B2	2/2010	Brand et al.	
7,819,075	B2	10/2010	Bowman et al.	
7,832,351	B2	11/2010	Bonney et al.	
8,418,690	B2	4/2013	Power	
8,459,253	B2	6/2013	Howgill	
8,474,448	B2	7/2013	Oi	
8,511,302	B2	8/2013	Parkes	
8,662,381	B2	3/2014	Kaar et al.	
8,978,966	B2	3/2015	Walsh et al.	
9,174,013	B2	11/2015	Walsh et al.	
9,216,261	B2	12/2015	Kaar et al.	
9,265,901	B2	2/2016	Lawrence et al.	
9,463,289	B2	10/2016	Walsh et al.	
9,533,111	B2	1/2017	Walsh et al.	
9,737,674	B2	8/2017	Walsh et al.	
9,808,587	B2	11/2017	Walsh et al.	
2002/0047021	A1	4/2002	Blacker	
2002/0078949	A1	6/2002	OLeary	
2002/0078950	A1	6/2002	OLeary	
2002/0084891	A1	7/2002	Mankins et al.	
2003/0209239	A1	11/2003	Rand	
2004/0089298	A1	5/2004	Haikarainen et al.	
2004/0095746	A1	5/2004	Murphy	
2005/0028815	A1	2/2005	Deaton	
2005/0087191	A1	4/2005	Morton	
2005/0126469	A1	6/2005	Lu	
2006/0096594	A1	5/2006	Bonney	
2006/0107949	A1	5/2006	Davies	
2006/0107979	A1	5/2006	Kim	
2007/0062518	A1	3/2007	Geser	
2007/0240712	A1	10/2007	Fleming et al.	
2007/0241025	A1	10/2007	Parkes	
2007/0246042	A1	10/2007	Purkins	
2008/0035144	A1	2/2008	Bowman et al.	
2008/0156321	A1	7/2008	Bowman et al.	
2008/0242465	A1	10/2008	Strobel	
2009/0178678	A1	7/2009	OLeary	
2010/0078490	A1	4/2010	Fenlon	
2010/0089395	A1	4/2010	Power	
2010/0218759	A1	9/2010	Anderson	
2011/0041845	A1	2/2011	Solomon	
2012/0006322	A1	1/2012	Anderson	
2012/0247458	A1	10/2012	Lawrence et al.	

FOREIGN PATENT DOCUMENTS

CN	1956448	5/2007
CN	101198972	6/2008
EP	1330280	7/2003
EP	1486227	12/2004
GB	2320489	6/1998
GB	2348928	10/2001
IL	201256	11/2014
JP	02502129	7/1990
JP	450059	8/1992
JP	07100205	4/1995
JP	10504220	4/1998
JP	2002528144	9/2002
JP	2004501685	1/2004
JP	2007534378	11/2007
JP	2008-94103 A	4/2008
JP	2008094103	4/2008
JP	2008261423	10/2008
JP	2009233308	10/2009
JP	2009257392	11/2009
JP	2010096308	4/2010
WO	8909078	10/1989
WO	9209324	6/1992
WO	9628205	9/1996
WO	9828033	7/1998
WO	9856444	12/1998
WO	9936115	7/1999
WO	01/28887	4/2001
WO	2001087391	11/2001
WO	02/00281 A2	1/2002
WO	03101514	12/2003
WO	2005060535	7/2005
WO	2005060917	7/2005
WO	2005102430	11/2005
WO	2006062449	6/2006
WO	2006062449 A1	6/2006
WO	2006110080	10/2006
WO	2007012861	2/2007
WO	2007062518	6/2007
WO	2008023019	2/2008
WO	2008119552	2/2008
WO	2008121459	10/2008
WO	2011012325	2/2011
WO	2011012327	2/2011

OTHER PUBLICATIONS

English Translation of Chinese Office Action, corresponds to CN201080041218.1.
English Translation of Chinese Office Action, corresponds to CN201080040988.4.
European Search report for EP Application No. 13004775.6.
European Search report for EP Application No. 13005367.1.
File History for U.S. Appl. No. 14/713,633.

(56) **References Cited**

OTHER PUBLICATIONS

Final OA for U.S. Appl. No. 13/387,532.
Final OA for U.S. Appl. No. 14/876,190.
International Search Report for PCT/EP10/04790.
International Search Report for PCT/EP10/04791.
International Search Report for PCT/EP10/04792.
Office Action issued by the Israel Patent Office dated Jul. 3, 2017 in reference to Israel Patent Application No. 247396, 3 pages.
Office Action issued by the Israel Patent Office dated Jul. 27, 2017 in reference to Israel Patent Application No. 247402, 4 pages.
Final Office Action dated Oct. 20, 2016 for U.S. Appl. No. 14/699,567.
Non-Final Office Action dated Jan. 12, 2017 for U.S. Appl. No. 14/713,620, 8 pages.
Final Rejection dated Sep. 27, 2016 for U.S. Appl. No. 14/699,578.
Final Office Action dated Aug. 31, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Advisory action dated Feb. 9, 2017 for U.S. Appl. No. 14/699,584.
Non-final rejection dated Jul. 12, 2016 for U.S. Appl. No. 14/713,643.
File History for U.S. Appl. No. 15/271,738.
File History for U.S. Appl. No. 15/269,102.
File History for U.S. Appl. No. 15/262,818.
File History for U.S. Appl. No. 15/289,553.
File History for U.S. Appl. No. 15/269,249.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/699,584.
Non-Final Office Action dated Jun. 24, 2016 for U.S. Appl. No. 14/713,620, 7 pages.
Final rejection dated Oct. 20, 2016 or U.S. Appl. No. 14/713,633.
Advisory Action dated Mar. 16, 2017 or U.S. Appl. No. 14/713,633.
Entire patent prosecution history of U.S. Appl. No. 13/110,532, filed, May 18, 2011, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,324, filed, Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,343, filed, Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,353, filed, Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,363, filed, Dec. 1, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/103,392, filed, Dec. 11, 2013, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/699,567, filed, Apr. 29, 2015, entitled, "Dose Counter for Inhaler and Method for Counting Doses.".
Entire patent prosecution history of U.S. Appl. No. 14/699,578, filed, Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having a Bore !And Shaft Arrangement.".
Entire patent prosecution history of U.S. Appl. No. 14/699,584, filed, Apr. 29, 2015, entitled, "Dose Counter for Inhaler Having an Antireverse Rotation Actuator.".
Entire patent prosecution history of U.S. Appl. No. 14/713,612, filed, May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/713,620, filed, May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
Entire patent prosecution history of U.S. Appl. No. 14/713,643, filed, May 15, 2015, entitled, "Dose Counters for Inhalers, Inhalers and Methods of Assembly Thereof.".
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 211.8.
European Patent Office Communication, dated Apr. 24, 2014 of counterpart European Patent Application No. 11 010 212.6.
First Examination Report of counterpart New Zealand Patent Application No. 603466, dated Jul. 1, 2013.
File history for U.S. Appl. No. 13/387,508.
File history for U.S. Appl. No. 13/387,532.
File history for U.S. Appl. No. 13/388,535.
File history for U.S. Appl. No. 14/132,918.
File history for U.S. Appl. No. 14/876,190.
File history for U.S. Appl. No. 14/967,905.
Office Action, Israel Application No. IL263904 dated Sep. 14, 2021, 4 pgs.

* cited by examiner

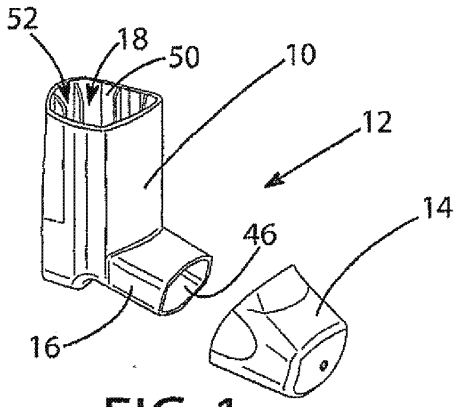


FIG. 1

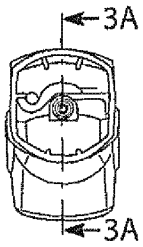


FIG. 2

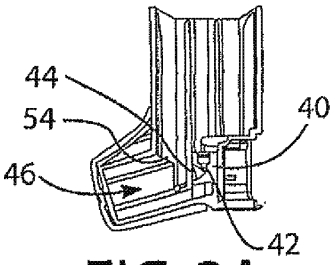


FIG. 3A

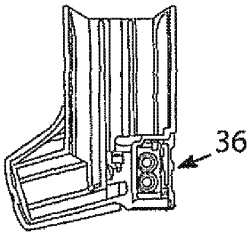


FIG. 3B

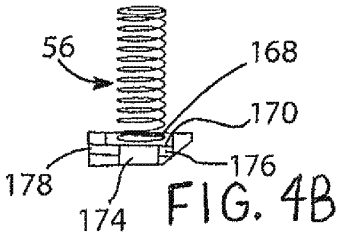


FIG. 4B

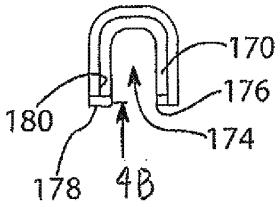


FIG. 4C

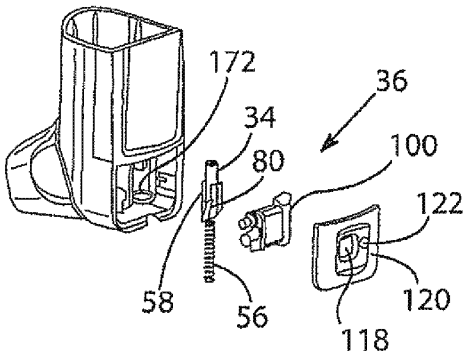


FIG. 4A

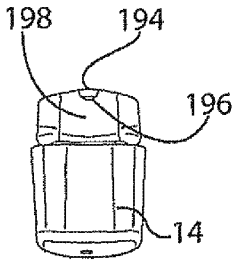


FIG. 5

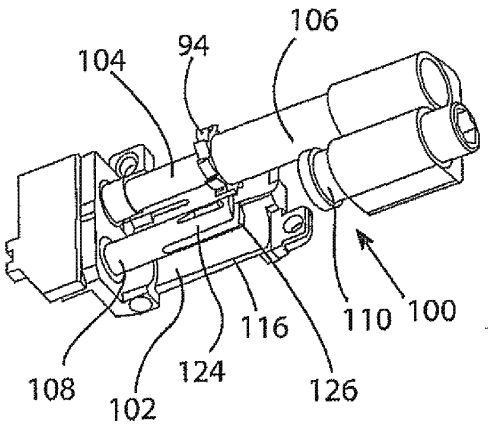


FIG. 6A

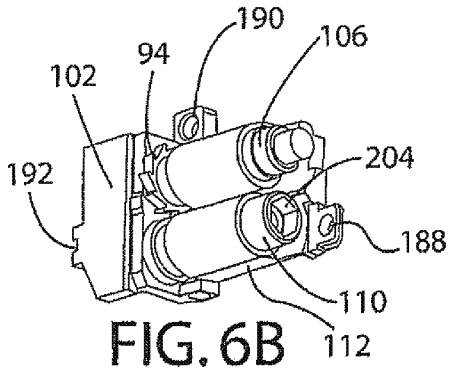


FIG. 6B

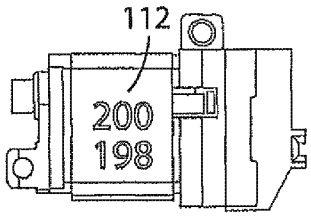


FIG. 6C

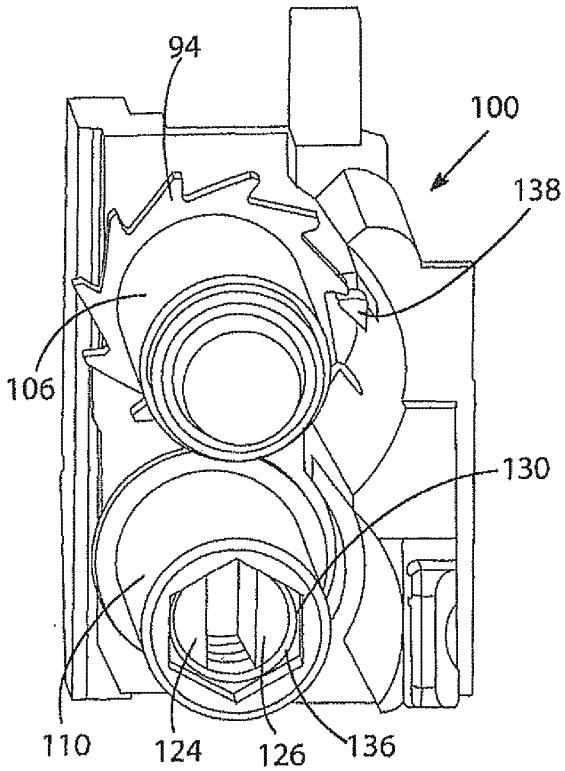


FIG. 6D

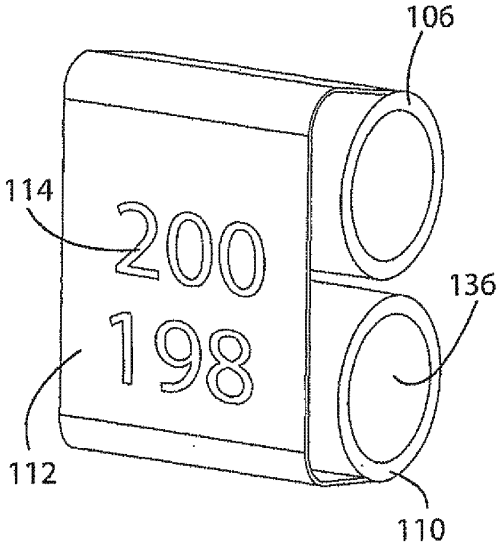


FIG. 6E

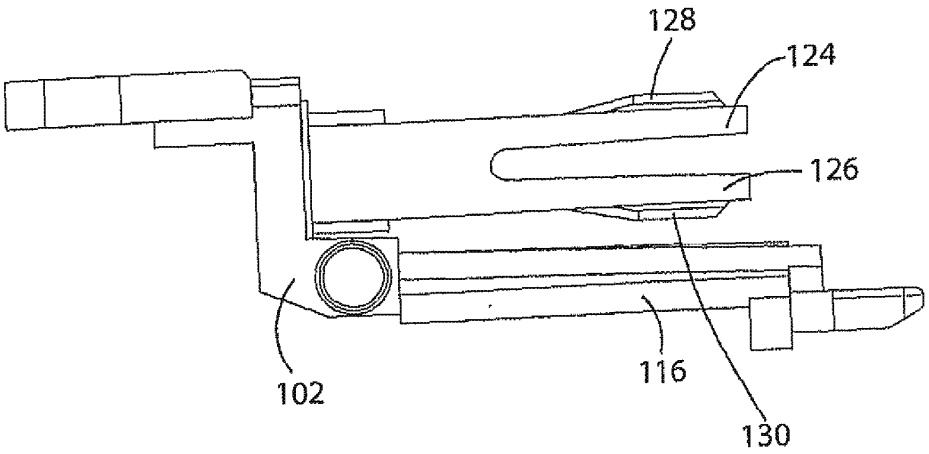


FIG. 6F

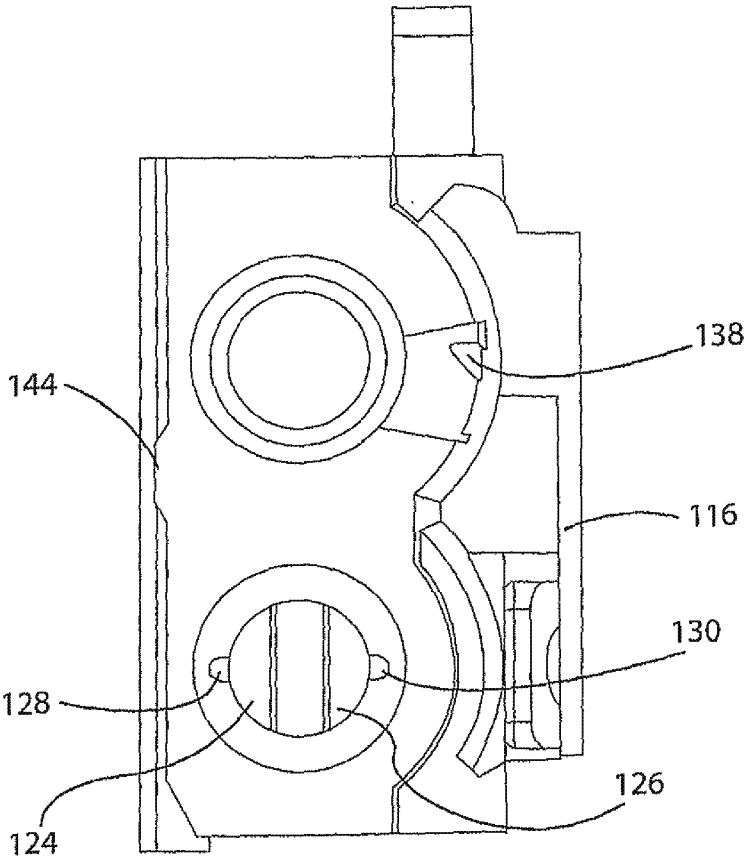


FIG. 6G

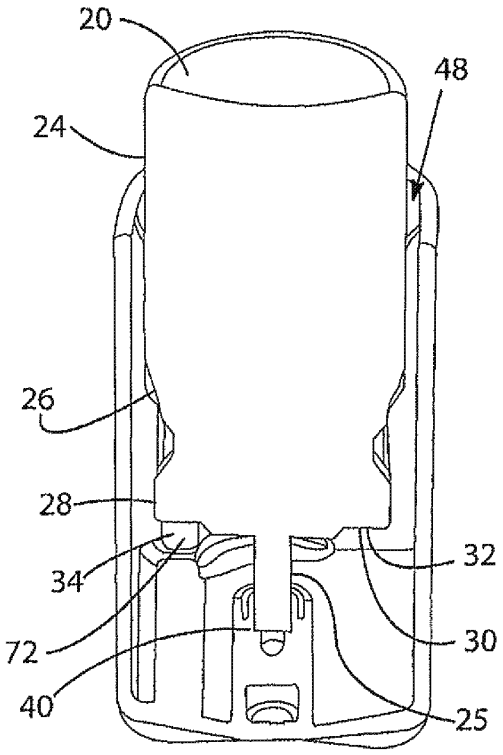


FIG. 7A

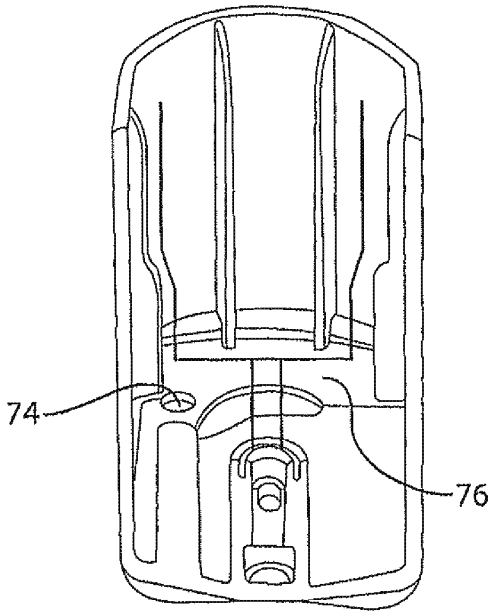


FIG. 7B

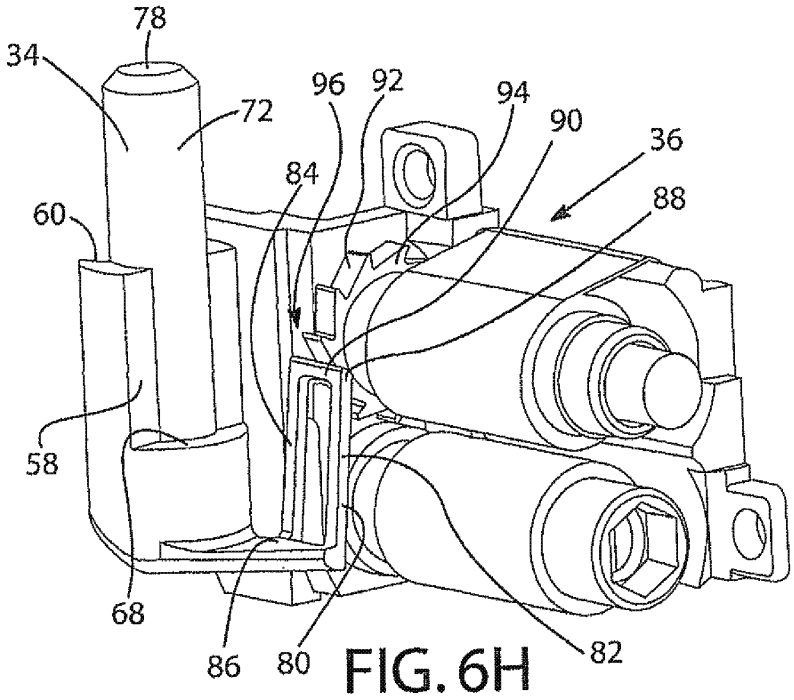


FIG. 6H

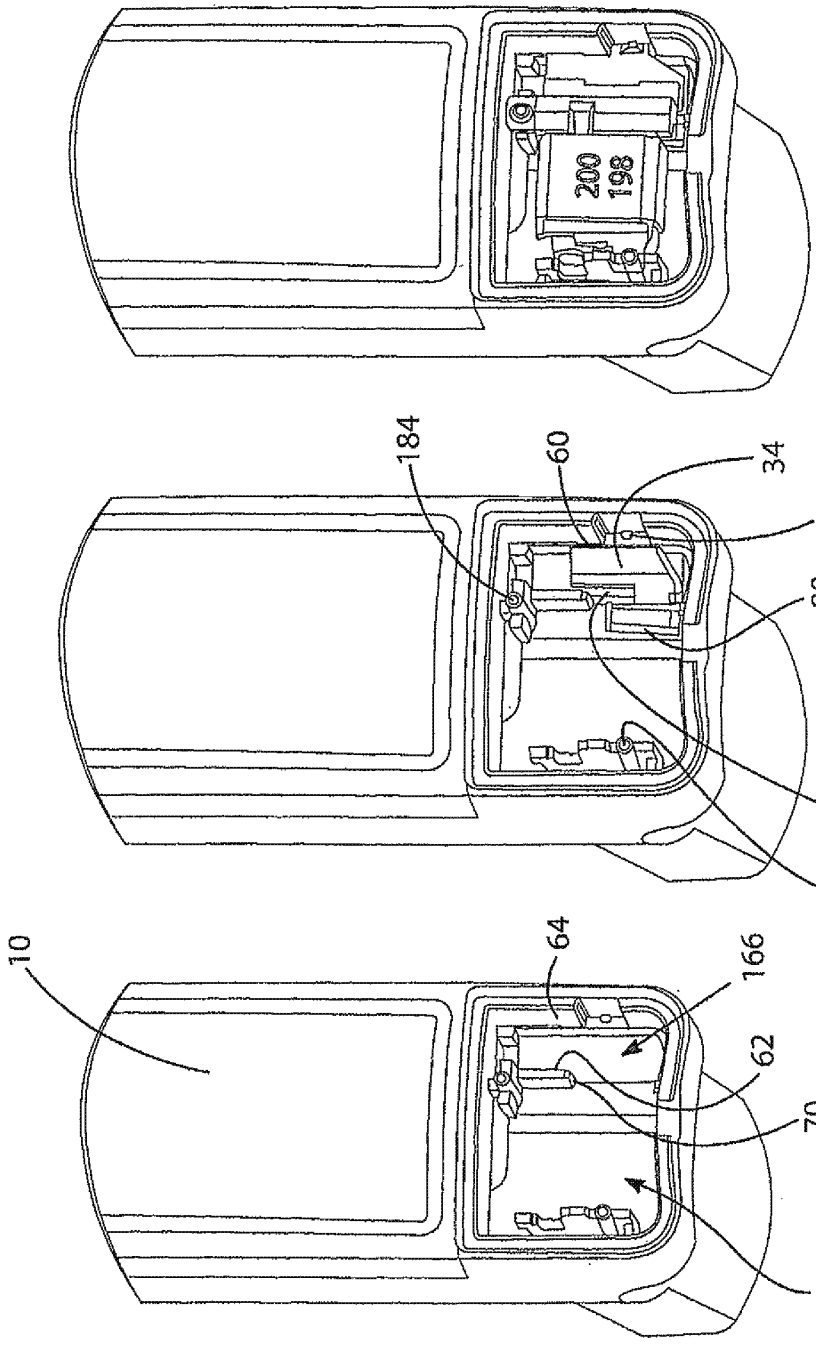


FIG. 8C

FIG. 8B

FIG. 8A

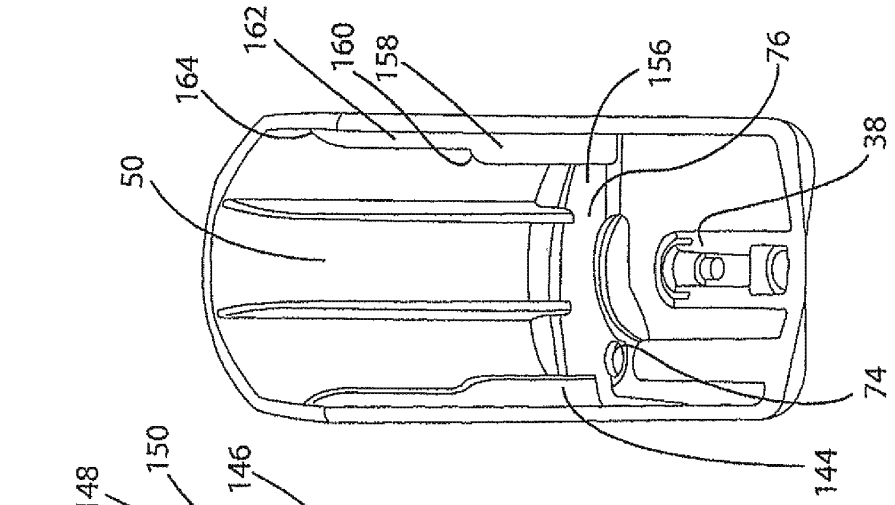


FIG. 7C

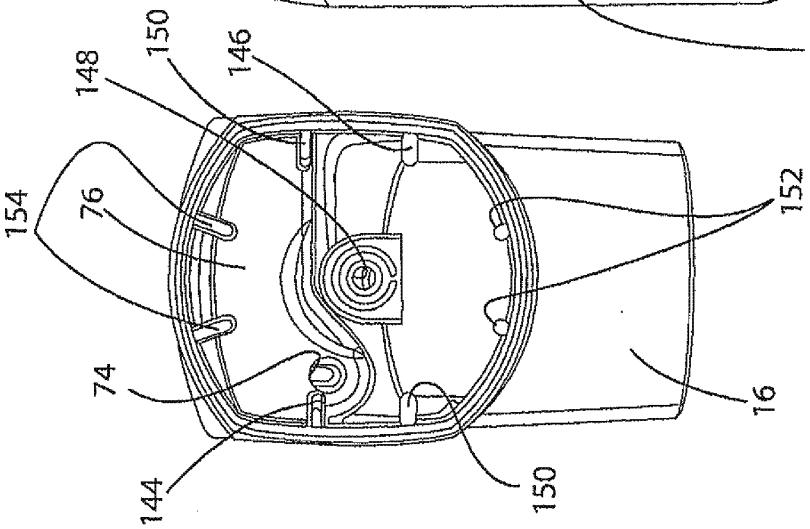


FIG. 7D

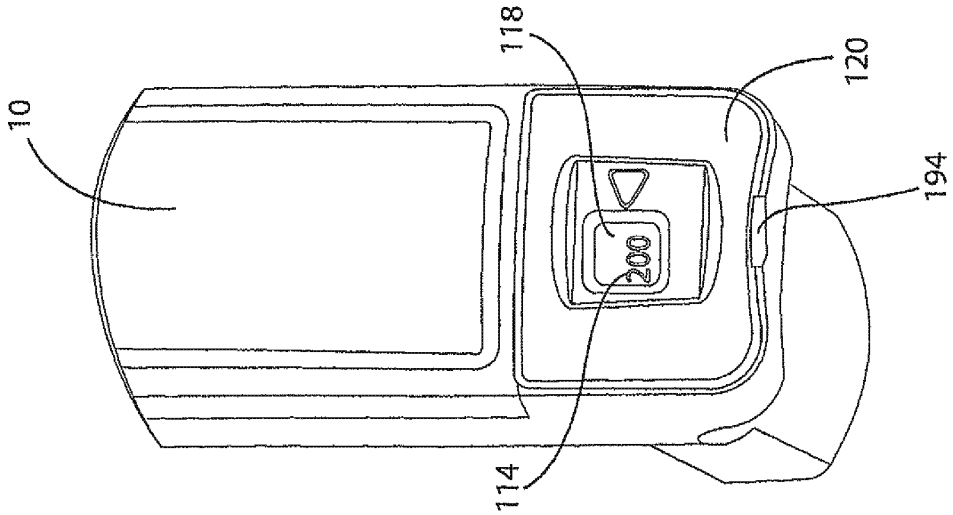


FIG. 8D

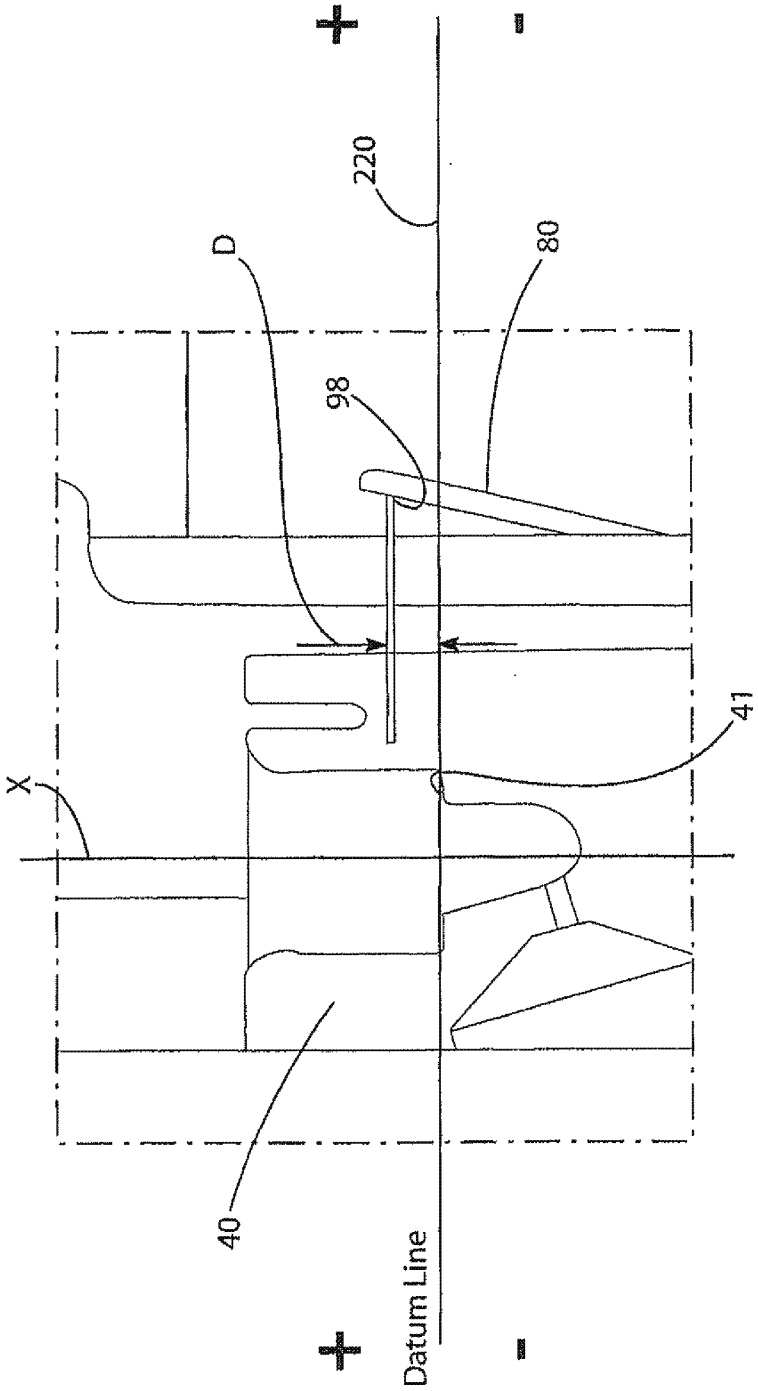


FIG. 9

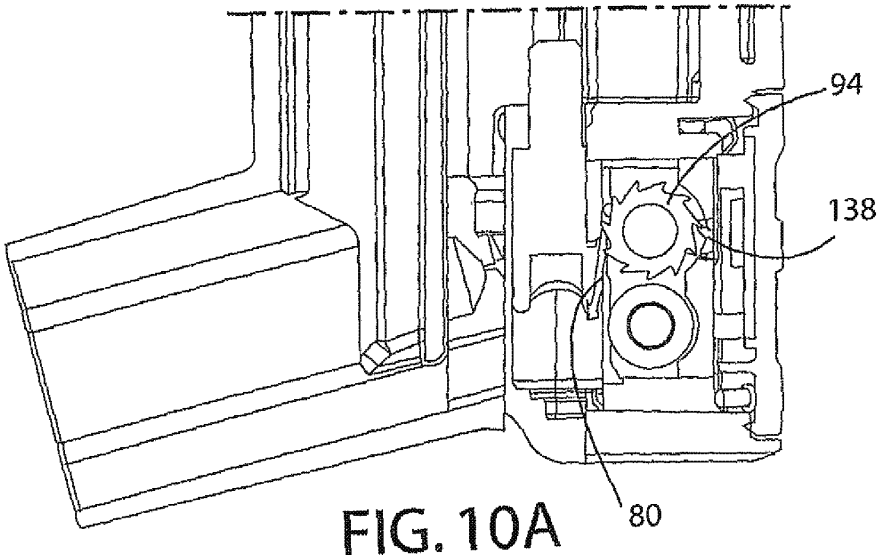


FIG. 10A

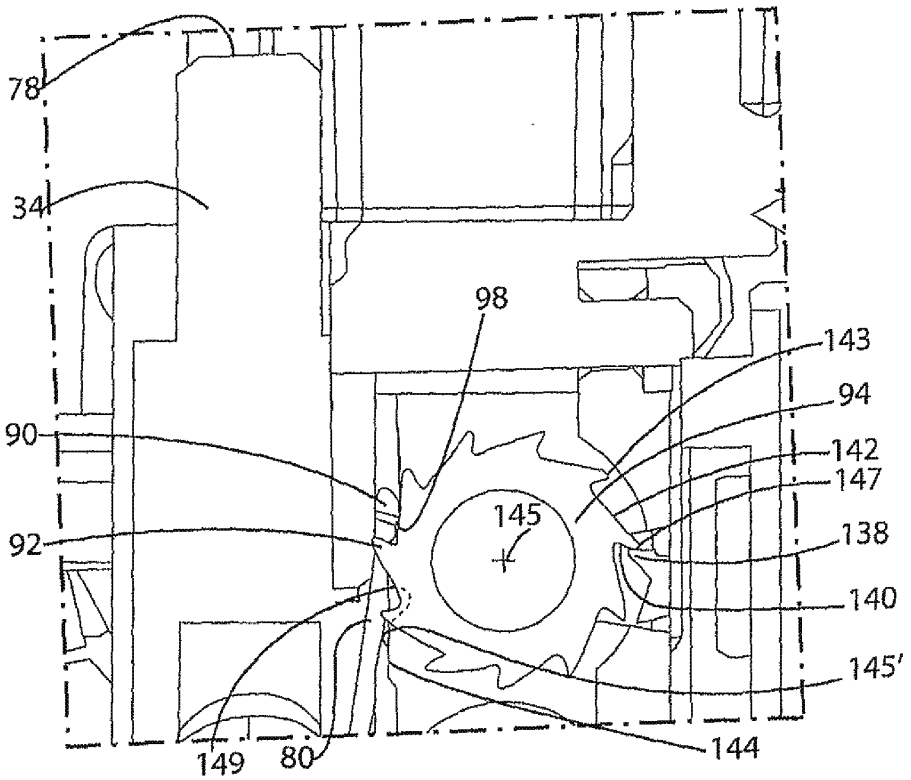


FIG. 10B

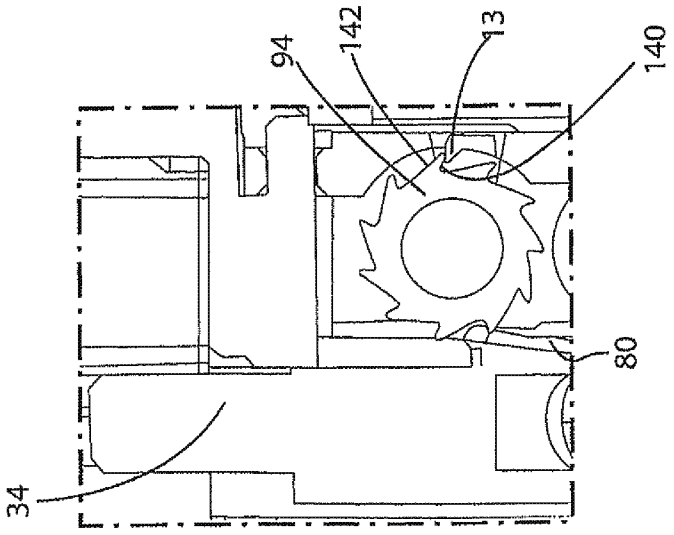


FIG. 10E

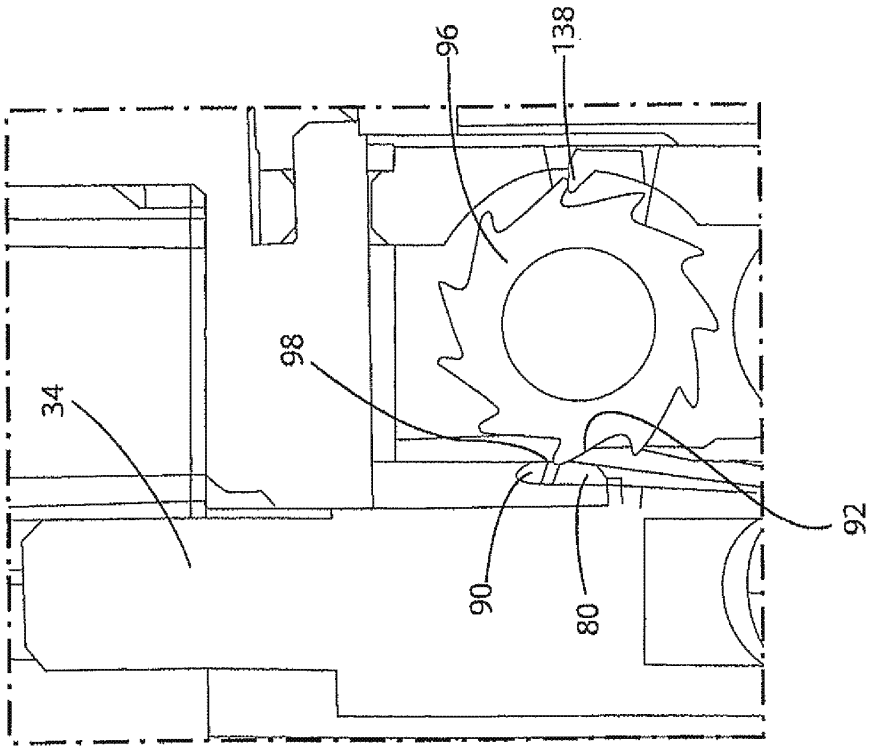


FIG. 10C

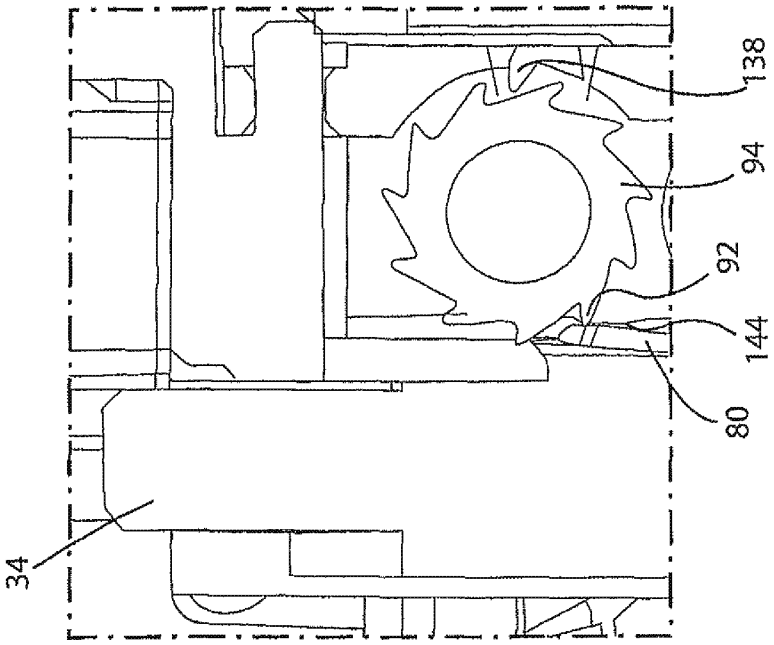


FIG. 10F

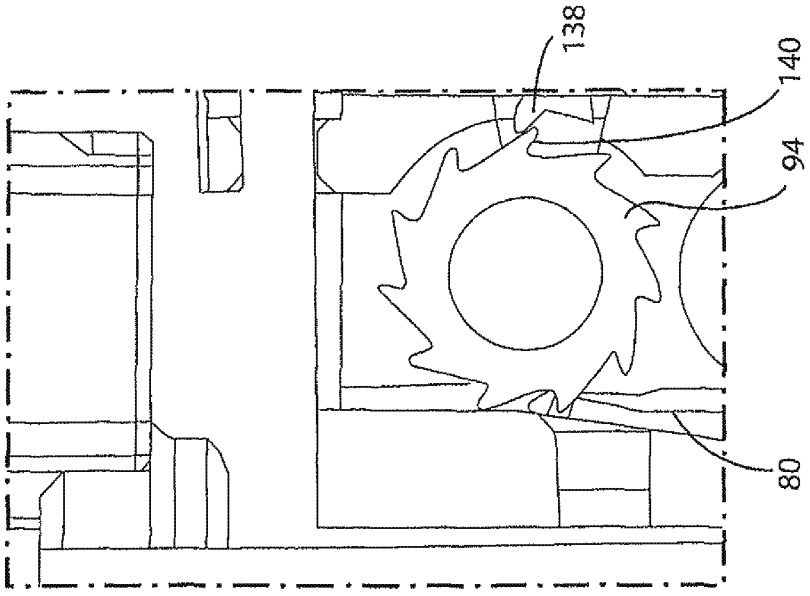


FIG. 10D

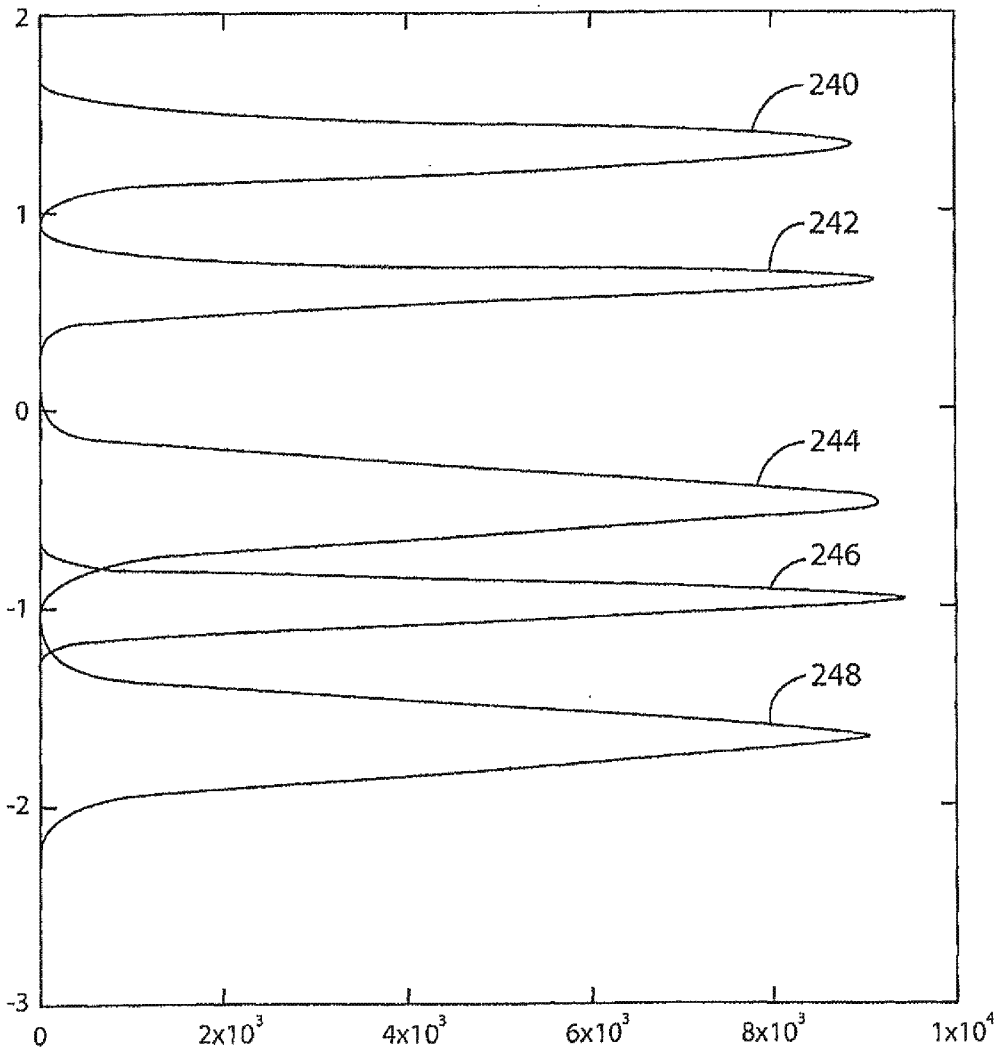

2
1
0
-1
-2
-3
0
2x10^3
4x10^3
6x10^3
8x10^3
1x10^4
240
242
244
246
248

FIG. 11

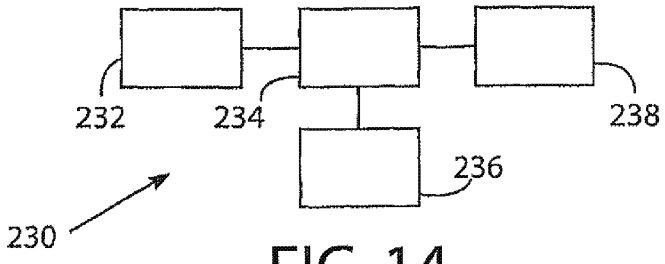

232
234
236
238
230

FIG. 14

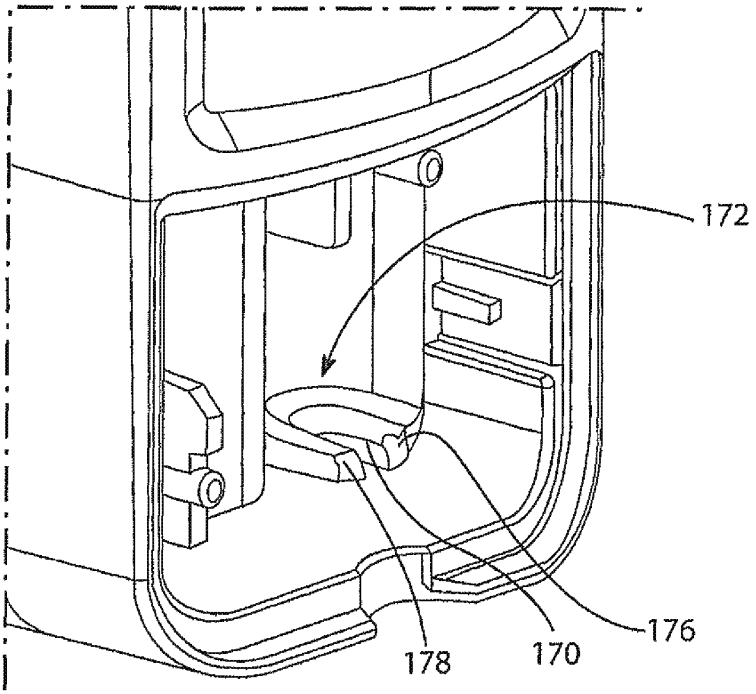


FIG. 12

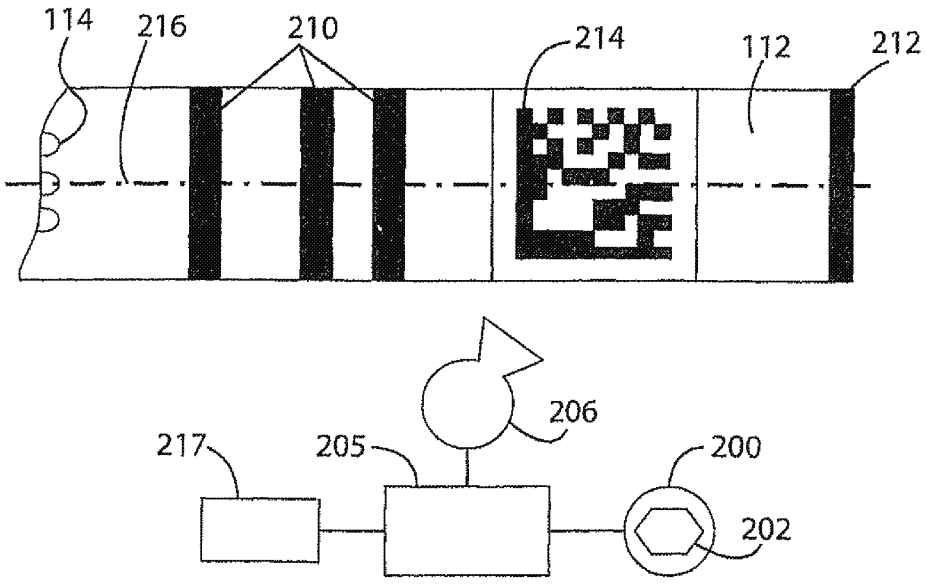


FIG. 13

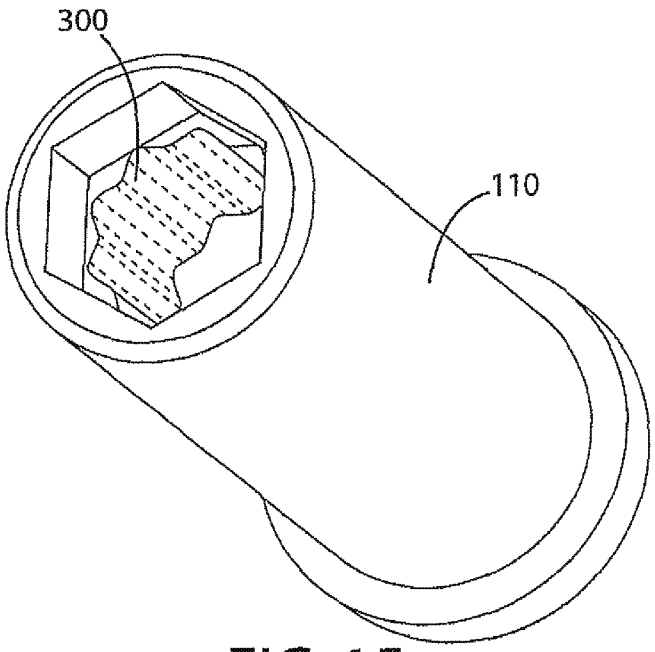


FIG. 15

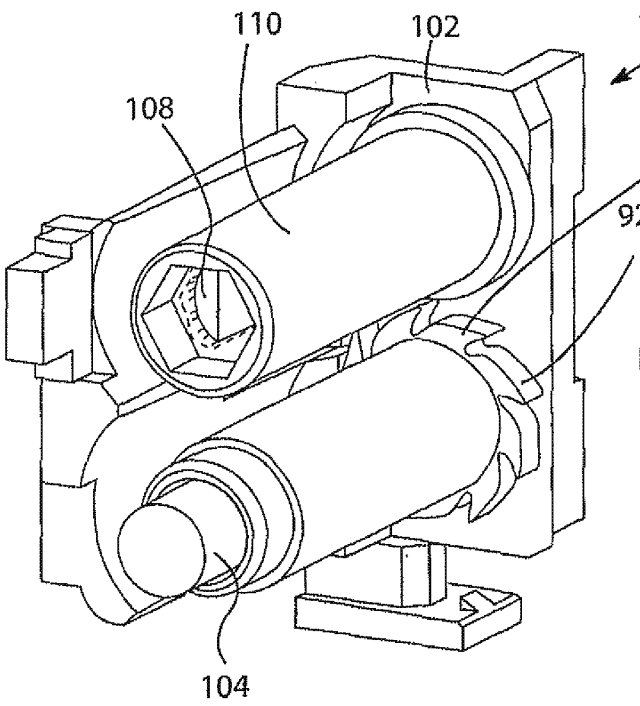


FIG. 20

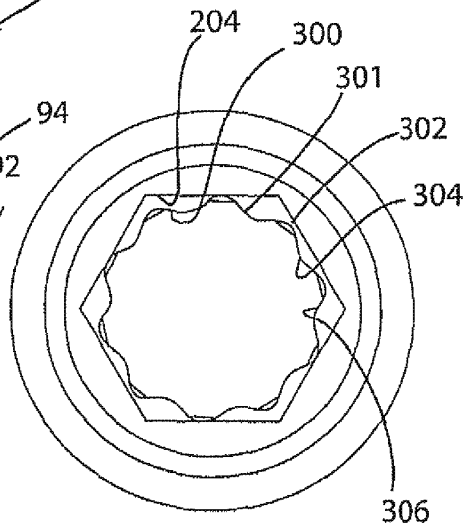


FIG. 16

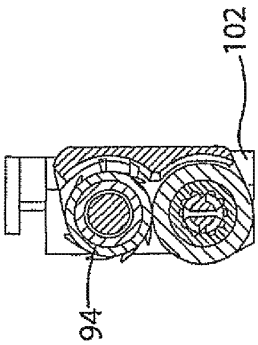


FIG. 19A

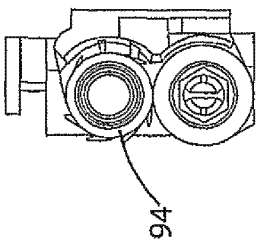


FIG. 19B

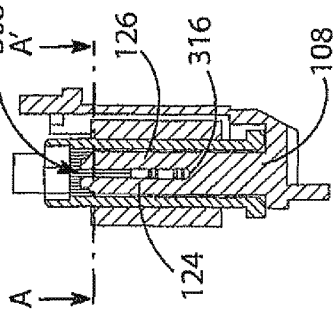


FIG. 19C

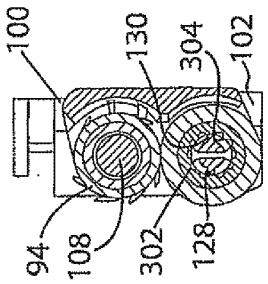


FIG. 18A

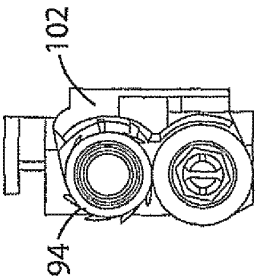


FIG. 18B

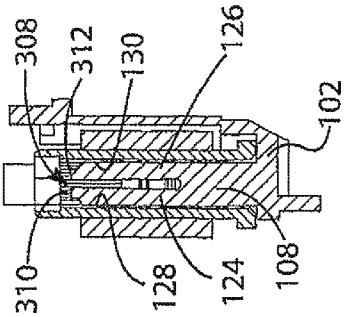


FIG. 18C

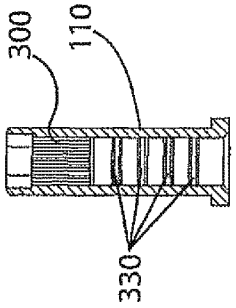


FIG. 17

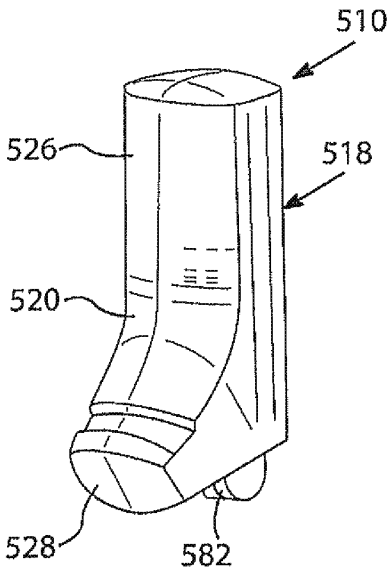

510
526
518
520
528
582

FIG. 21

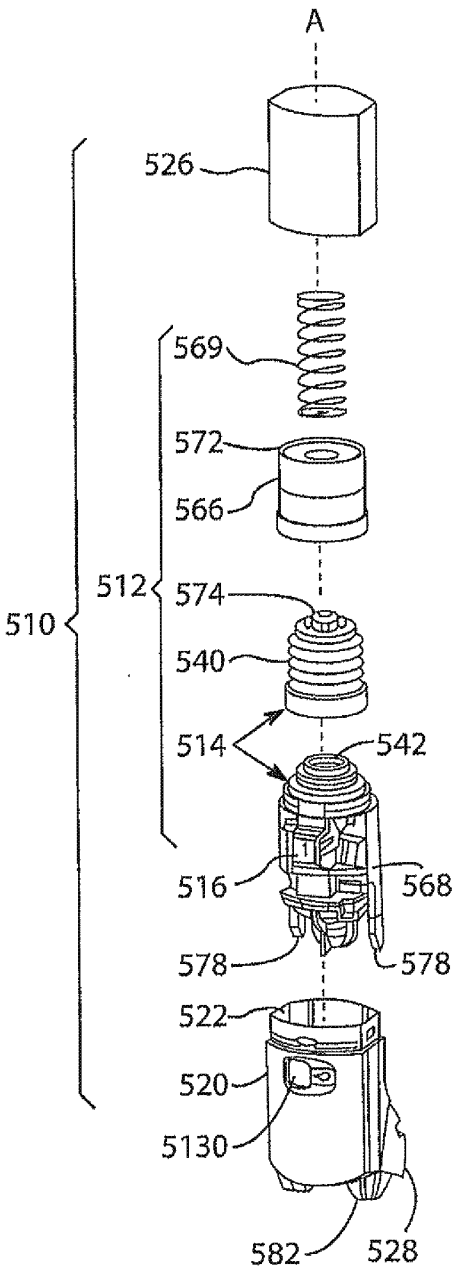

A
526
569
572
566
512
574
510
540
514
542
516
568
578
578
522
520
5130
582
528

FIG. 22

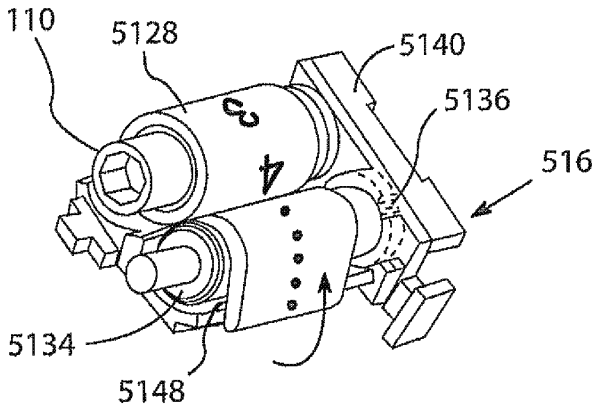

110
5128
5140
5136
516
5134
5148

FIG. 23

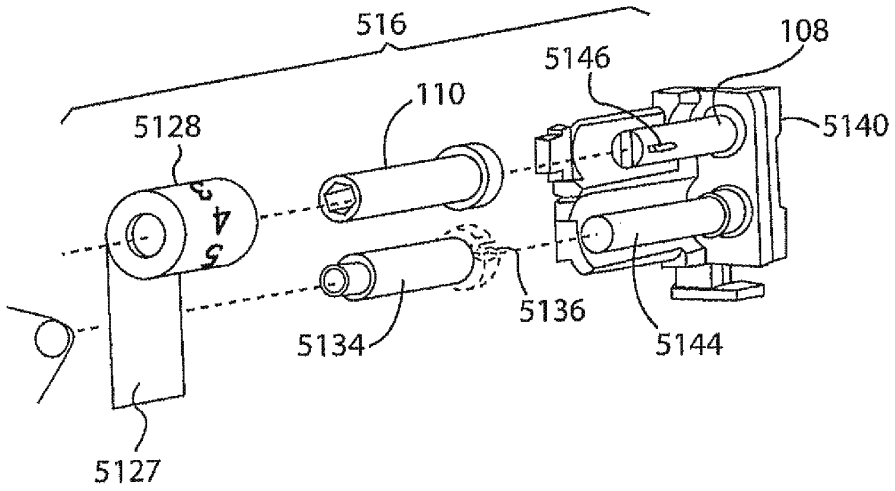

516
108
5146
110
5128
5140
5136
5134
5144
5127

FIG. 24

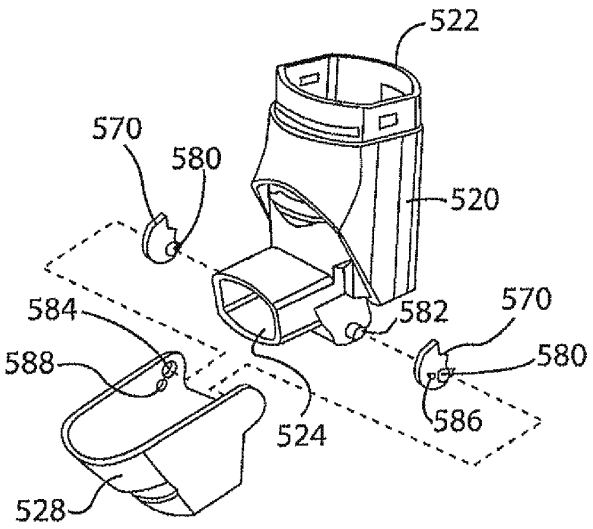


FIG. 25

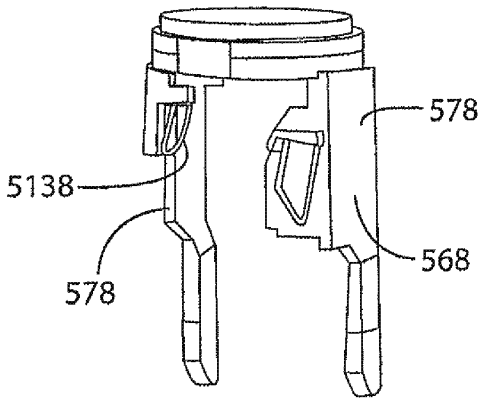


FIG. 26

DOSE COUNTER FOR INHALER HAVING AN ANTI-REVERSE ROTATION ACTUATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation patent application of U.S. patent application Ser. No. 15/804,735 filed Nov. 6, 2017, which is a continuation of U.S. patent application Ser. No. 15/269,249, filed Sep. 19, 2016, now U.S. Pat. No. 9,808,587, which is a continuation of U.S. patent application Ser. No. 14/103,324, filed Dec. 11, 2013, now U.S. Pat. No. 9,463,289, which is a divisional patent application of U.S. patent application Ser. No. 13/110,532, filed May 18, 2011, now U.S. Pat. No. 8,978,966, which claims priority to U.S. Patent Application No. 61/345,763, filed May 18, 2010, and U.S. Patent Application No. 61/417,659, filed Nov. 29, 2010, each of which is incorporated herein by reference in its entirety for any and all purposes.

FIELD OF THE INVENTION

The present invention relates to dose counters for inhalers, inhalers and methods of assembly thereof. The invention is particularly applicable to metered dose inhalers including dry power medicament inhalers, breath actuated inhalers and manually operated metered dose medicament inhalers.

BACKGROUND OF THE INVENTION

Metered dose inhalers can comprise a medicament-containing pressurised canister containing a mixture of active drug and propellant. Such canisters are usually formed from a deep-dawn aluminium cup having a crimped lid which carries a metering valve assembly. The metering valve assembly is provided with a protruding valve stem which, in use is inserted as a push fit into a stem block in an actuator body of an inhaler having a drug delivery outlet. In order to actuate a manually operable inhaler, the user applies by hand a compressive force to a closed end of the canister and the internal components of the metering valve assembly are spring loaded so that a compressive force of approximately 15 to 30N is required to activate the device in some typical circumstances.

In response to this compressive force the canister moves axially with respect to the valve stem and the axial movement is sufficient to actuate the metering valve and cause a metered quantity of the drug and the propellant to be expelled through the valve stem. This is then released into a mouthpiece of the inhaler via a nozzle in the stem block, such that a user inhaling through the outlet of the inhaler will receive a dose of the drug.

A drawback of self-administration from an inhaler is that it is difficult to determine how much active drug and/or propellant are left in the inhaler, if any, especially of the active drug and this is potentially hazardous for the user since dosing becomes unreliable and backup devices not always available.

Inhalers incorporating dose counters have therefore become known.

WO 98/028033 discloses an inhaler having a ratchet mechanism for driving a tape drive dose counter. A shaft onto which tape is wound has a friction clutch or spring for restraining the shaft against reverse rotation.

EP-A-1486227 discloses an inhaler for dry powered medicament having a ratchet mechanism for a tape dose counter which is operated when a mouthpiece of the inhaler

is closed. Due to the way in which the mouthpiece is opened and closed, and actuation pawl of the device which is mounted on a yoke, travels a known long stroke of consistent length as the mouthpiece is opened and closed.

WO 2008/119552 discloses a metered-dose inhaler which is suitable for breath-operated applications and operates with a known and constant canister stroke length of 3.04 mm+/−0.255 mm. A stock bobbin of the counter, from which a tape is unwound, rotates on a shaft having a split pin intended to hold the stock bobbin taut. However, some dose counters do not keep a particularly reliable count, such as if they are dropped onto a hard surface.

More recently, it has become desirable to improve dose counters further and, in particular, it is felt that it would be useful to provide extremely accurate dose counters for manually-operated canister-type metered dose inhalers. Unfortunately, in these inhalers, it has been found in the course of making the present invention that the stroke length of the canister is to a very large extent controlled on each dose operation by the user, and by hand. Therefore, the stroke length is highly variable and it is found to be extremely difficult to provide a highly reliable dose counter for these applications. The dose counter must not count a dose when the canister has not fired since this might wrongly indicate to the user that a dose has been applied and if done repeatedly the user would throw away the canister or whole device before it is really time to change the device due to the active drug and propellant reaching a set minimum. Additionally, the canister must not fire without the dose counter counting because the user may then apply another dose thinking that the canister has not fired, and if this is done repeatedly the active drug and/or propellant may run out while the user thinks the device is still suitable for use according to the counter. It has also been found to be fairly difficult to assembly some known inhaler devices and the dose counters therefor. Additionally, it is felt desirable to improve upon inhalers by making them easily usable after they have been washed with water.

The present invention aims to alleviate at least to a certain extent one or more of the problems of the prior art.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a counter display arranged to indicate dosage information, a drive system arranged to move the counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

The regulator is advantageous in that it helps prevent unwanted motion of the counter display if the counter is dropped.

According to a further aspect of the present invention, the regulator provides a resistance force of greater than 0.1 N against movement of the counter display. According to still a further aspect of the present invention, the resistance force is greater than 0.3 N. According to yet a further aspect of the present invention, the resistance force is from 0.3 to 0.4 N.

Preferably, the counter comprises a tape.

Preferably, the tape has dose counter indicia displayed thereon. The first station may comprise a region of the dose counter where tape is held which is located before a display location, such as a display window, for the counter indicia.

The first station may comprise a first shaft, the tape being arranged on the first shaft and to unwind therefrom upon movement of the counter display.

The first shaft may be mounted for rotation relative to a substantially rotationally fixed element of the dose counter.

The regulator may comprise at least one projection which is arranged on one of the first shaft and the substantially rotationally fixed element and to engage incrementally with one or more formations on the other of the first shaft and the substantially rotationally fixed element.

At least two said projections may be provided. Exactly two said projections maybe provided.

Each projection may comprise a radiused surface.

The at least one projection may be located on the substantially fixed element which may comprise a fixed shaft which is fixed to a main body of the dose counter, the first shaft being rotationally mounted to the fixed shaft.

Preferably, the fixed shaft has at least two resiliently flexible legs (or forks). Each leg may have at least one said projection formed in an outwardly facing direction thereon, said one or more formations being formed on an inwardly facing engagement surface of the first shaft, said at least one projection being arranged to resiliently engage said one or more formations. Preferably, a series of said formations are provided. An even number of said formations may be provided. Eight to twelve of said formations may be provided. In one embodiment, ten said formations are provided.

Each said formation may comprise a concavity formed on an engagement surface. Each concavity may comprise a radiused surface wall portion which preferably merges on at least one side thereof into a flat wall portion surface. The engagement surface may include a series of said concavities, and convex wall portions of the engagement surface may be formed between each adjacent two said concavities, each said convex wall portion comprising a convex radiused wall portion.

Each convex radiused wall portion of each convex wall portion may be connected by said flat wall portion surfaces to each adjacent concavity.

The fixed shaft may comprise a split pin with fork legs and each projection may be located on a said fork leg.

The first shaft may comprise a substantially hollow bobbin.

Said at least one formation may be located on an inner surface of the bobbin. In other embodiments it may be located on an outer surface thereof. Said engagement surface may extend partially along said bobbin, a remainder of the respective inner or outer surface having a generally smooth journal portion along at least a portion thereof.

The drive system may comprise a tooth ratchet wheel arranged to act upon a second shaft which is located at the second station, the second shaft being rotatable to wind the tape onto the second shaft.

The second shaft may be located on a main body of the dose counter spaced from and parallel to the first shaft.

The ratchet wheel may be fixed to the second shaft is arranged to rotate therewith. The ratchet wheel may be secured to an end of the second shaft and aligned coaxially with the second shaft.

The dose counter may include anti-back drive system which is arranged to restrict motion of the second shaft. The anti-back drive system may include a substantially fixed tooth arranged to act upon teeth of the ratchet wheel.

According to a further aspect of the present invention, a dose counter includes an anti-back drive system which is arranged to restrict motion of the second shaft in a tape winding direction.

According to a further aspect of the present invention there is provided a shaft for holding counter tape in a dose counter for an inhaler, the shaft having an engagement surface including incrementally spaced formations located around a periphery thereof, the formations comprising a series of curved concavities and convex portions.

The shaft may comprise a hollow bobbin.

The engagement surface may be a generally cylindrical inwardly directed surface.

The engagement surface may include a flat surface wall portion joining each concavity and convex wall portion.

Each concavity may comprise a radiused wall portion.

Each convex wall portion may comprise a radiused wall portion.

Said concavities may be regularly spaced around a longitudinal axis of the shaft.

Said convex wall portions may be regularly spaced around a longitudinal axis of the shaft.

In some embodiments there may be from eight to twelve said concavities and/or convex wall portions regularly spaced around a longitudinal axis thereof.

One embodiment includes ten said concavities and/or convex wall portions regularly spaced around a longitudinal axis of the shaft.

According to a further aspect of the present invention there is provided a shaft and counter tape assembly for use in a dose counter for an inhaler, the assembly comprising a rotatable shaft and a counter tape which is wound around the shaft and is adapted to unwind therefrom upon inhaler actuation, the shaft having an engagement surface which includes incrementally spaced formations located around a periphery thereof.

According to a further aspect of the present invention there is provided an inhaler for the inhalation of medication and the like, the inhaler including a dose counter as in the first aspect of the present invention.

A preferred construction consists of a manually operated metered dose inhaler including a dose counter chamber including a dose display tape driven by a ratchet wheel which is driven in turn by an actuator pawl actuated by movement of a canister, the tape unwinding from a stock bobbin during use of the inhaler, a rotation regulator being provided for the stock bobbin and comprising a wavelike engagement surface with concavities which engage against control elements in the form of protrusions on resilient forks of a split pin thereby permitting incremental unwinding of the stock bobbin yet resisting excessive rotation if the inhaler is dropped onto a hard surface.

According to another aspect of the present invention there is provided a dose counter for a metered dose inhaler having a body arranged to retain a medicament canister of predetermined configuration for movement of the canister relative thereto; the dose counter comprising: an incremental counting system for counting doses, the incremental counting system having a main body, an actuator arranged to be driven in response to canister motion and to drive an incremental output member in response to canister motion, the actuator and incremental output member being configured to have predetermined canister fire and count configurations in a canister fire sequence, the canister fire configuration being determined by a position of the actuator relative to a datum at which the canister fires medicament and the count configuration being determined by a position of the actuator relative to the datum at which the incremental count system makes an incremental count, wherein the actuator is

arranged to reach a position thereof in the count configuration at or after a position thereof in the canister fire configuration.

This arrangement has been found to be highly advantageous since it provides an extremely accurate dose counter which is suitable for use with manually operated metered dose inhalers. It has been found that dose counters with these features have a failure rate of less than 50 failed counts per million full canister activation depressions. It has been found in the course of making the present invention that highly reliable counting can be achieved with the dose counter counting at or soon after the point at which the canister fires. It has been is covered by the present inventors that momentum and motion involved in firing the canister, and in some embodiments a slight reduction in canister back pressure on the user at the time of canister firing, can very reliably result in additional further motion past the count point.

The actuator and incremental counting system may be arranged such that the actuator is displaced less than 1 mm, typically 0.25 to 0.75 mm, more preferably about 0.4 to 0.6 mm, relative to the body between its location in the count and fire configurations, about 0.48 mm being preferred. The canister, which can move substantially in line with the actuator, can reliably move this additional distance so as to achieve very reliable counting.

The incremental count system may comprise a ratchet mechanism and the incremental output member may comprise a ratchet wheel having a plurality of circumferentially spaced teeth arranged to engage the actuator.

The actuator may comprise an actuator pawl arranged to engage on teeth of the ratchet wheel. The actuator pawl may be arranged to be connected to or integral with an actuator pin arranged to engage and be depressed by a medicament canister bottom flange. The actuator pawl may be generally U-shaped having two parallel arms arranged to pull on a central pawl member arranged substantially perpendicular thereto. This provides a very reliable actuator pawl which can reliably pull on the teeth of the ratchet wheel.

The incremental count system may include a tape counter having tape with incremental dose indicia located thereon, the tape being positioned on a tape stock bobbin and being arranged to unwind therefrom.

The actuator and incremental output member may be arranged to provide a start configuration at which the actuator is spaced from the ratchet output member, a reset configuration at which the actuator is brought into engagement with the incremental output member during a canister fire sequence, and an end configuration at which the actuator disengages from the ratchet output during a canister fire sequence.

The actuator may be arranged to be located about 1.5 to 2.0 mm, from its location in the fire configuration, when in the start configuration, about 1.80 mm being preferred.

The actuator may be arranged to be located about 1.0 to 1.2 mm, from its location in the fire configuration, when in the reset configuration, about 1.11 mm being preferred.

The actuator may be arranged to be located about 1.1 to 1.3 mm, from its location in the fire configuration, when in the end configuration, about 1.18 mm being preferred.

These arrangements provide extremely reliable dose counting, especially with manually operated canister type metered dose inhalers.

The main body may include a formation for forcing the actuator to disengage from the incremental output member when the actuator is moved past the end configuration. The formation may comprise a bumped up portion of an otherwise generally straight surface against which the actuator engages and along which it is arranged to slide during a canister firing sequence.

The dose counter may include a counter pawl, the counter pawl having a tooth arranged to engage the incremental output member, the tooth and incremental output member being arranged to permit one way only incremental relative motion therebetween. When the incremental output member comprises a ratchet wheel, the tooth can therefore serve as an anti-back drive tooth for the ratchet wheel, thereby permitting only one way motion or rotation thereof.

The counter pawl may be substantially fixedly mounted on the main body of the incremental count system and the counter pawl may be arranged to be capable of repeatedly engaging equi-spaced teeth of the incremental output member in anti-back drive interlock configurations as the counter is operated. The counter pawl may be positioned so that the incremental output member is halfway, or substantially halfway moved from one anti-back drive interlock configuration to the next when the actuator and incremental output member are in the end configuration thereof. This is highly advantageous in that it minimises the risk of double counting or non-counting by the dose counter.

According to a further aspect of the invention there is provided an inhaler comprising a main body arranged to retain a medicament canister of predetermined configuration and a dose counter mounted in the main body.

The inhaler main body may include a canister receiving portion and a separate counter chamber, the dose counter being located within the main body thereof, the incremental output member and actuator thereof inside the counter chamber, the main body of the inhaler having wall surfaces separating the canister-receiving portion and the counter chamber, the wall surfaces being provided with a communication aperture, an actuation member extending through the communication aperture to transmit canister motion to the actuator.

According to a further aspect of the present invention there is a provided an inhaler for metered dose inhalation, the inhaler comprising a main body having a canister housing arranged to retain a medicament canister for motion therein, and a dose counter, the dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of a medicament canister, wherein the canister housing has an inner wall, and a first inner wall canister support formation located directly adjacent the actuation member.

This is highly advantageous in that the first inner wall canister support formation can prevent a canister from rocking too much relative to the main body of the inhaler. Since the canister may operate the actuation member of the dose counter, this substantially improves dose counting and avoids counter errors.

The canister housing may have a longitudinal axis which passes through a central outlet port thereof, the central outlet port being arranged to mate with an outer canister fire stem of a medicament canister, the inner wall canister support formation, the actuation member and the outlet port lying in a common plane coincident with the longitudinal axis. Accordingly, this construction may prevent the canister from rocking towards the position of the dose counter actuation member, thereby minimising errors in counting.

The canister housing may have a further inner canister wall support formation located on the inner wall opposite, or substantially opposite, the actuation member. Accordingly, the canister may be supported against rocking motion away from the actuator member so as to minimise count errors.

The canister housing may be generally straight and tubular and may have an arrangement in which each said inner wall support formation comprises a rail extending longitudinally along the inner wall.

Each said rail may be stepped, in that it may have a first portion located towards a medicine outlet end or stem block of the canister housing which extends inwardly a first distance from a main surface of the inner wall and a second portion located toward an opposite end of the canister chamber which extends inwardly a second, smaller distance from the main surface of the inner wall. This may therefore enable easy insertion of a canister into the canister housing such that a canister can be lined up gradually in step wise function as it is inserted into the canister housing.

The inhaler may include additional canister support rails which are spaced around an inner periphery of the inner wall of the canister housing and which extend longitudinally therealong.

At least one of the additional rails may extend a constant distance inwardly from the main surface of the inner wall.

At least one of the additional rails may be formed with a similar configuration to the first inner wall canister support formation.

The dose counter may, apart from said at least a portion of the actuation member, be located in a counter chamber separate from the canister housing, the actuation member comprising a pin extending through an aperture in a wall which separates the counter chamber and the canister housing.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicaments having: a body for retaining a medicament store; the body including a dose counter, the dose counter having a moveable actuator and a return spring for the actuator, the return spring having a generally cylindrical and annular end; the body having a support formation therein for supporting said end of the return spring, the support formation comprising a shelf onto which said end is engageable and a recess below the shelf.

This shelf and recess arrangement is highly advantageous since it allows a tool (such as manual or mechanical tweezers) to be used to place the return spring of the actuator onto the shelf with the tool then being withdrawn at least partially via the recess.

The shelf may be U-shaped.

The support formation may include a U-shaped upstanding wall extending around the U-shaped shelf, the shelf and upstanding wall thereby forming a step and riser of a stepped arrangement.

The recess below the shelf my also be U-shaped.

At least one chamfered surface may be provided at an entrance to the shelf. This may assist in inserting the actuator and return spring into position.

A further aspect of the invention provides a method of assembly of an inhaler which includes the step of locating said end of said spring on the shelf with an assembly tool and then withdrawing the assembly tool at least partly via the recess. This assembly method is highly advantageous compared to prior art methods in which spring insertion has been difficult and in which withdrawal of the tool has sometimes accidentally withdrawn the spring again.

The cylindrical and annular end of the spring may be movable in a direction transverse to its cylindrical extent into the shelf while being located thereon.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament, the inhaler having a body for retaining a medicament store; and a dose counter, the dose counter having a moveable actuator and a chassis mounted on the body; the chassis being heat staked in position on the body. This is be highly advantageous in that the chassis can be very accurately positioned and held firmly in place, thereby further improving counting accuracy compared to prior art arrangements in which some movement of the chassis relative to the body may be tolerated in snap-fit connections.

The chassis may have at least one of a pin or aperture heat staked to a respective aperture or pin of the body.

The chassis may have a ratchet counter output member mounted thereon.

The ratchet counter output member may comprise a ratchet wheel arranged to reel in incrementally a dose meter tape having a dosage indicia located thereon.

According to a further aspect of the present invention there is provided a method of assembling an inhaler including the step of heat staking the chassis onto the body. The step of heat staking is highly advantageous in fixedly positioning the chassis onto the body in order to achieve highly accurate dose counting in the assembled inhaler.

The method of assembly may include mounting a spring-returned ratchet actuator in the body before heat staking the chassis in place. The method of assembly may include pre-assembling the chassis with a dose meter tape prior to the step of heat staking the chassis in place. The method of assembly may include attaching a dose meter cover onto the body after the heat staking step. The cover may be welded onto the body or may in some embodiments be glued or otherwise attached in place.

According to a further aspect of the present invention there is provided an inhaler for inhaling medicament and having a body, the body have a main part thereof for retaining a medicament store; and a dose counter, the dose counter being located in a dose counter chamber of the body which is separated from the main part of the body, the dose counter chamber of the body having a dosage display and being perforated so as to permit the evaporation of water or aqueous matter in the dose counter chamber into the atmosphere.

This is high advantageous since it enables the inhaler to be thoroughly washed and the dose counting chamber can thereafter dry out fully.

The display may comprise a mechanical counter display inside the dose counter chamber and a window for viewing the mechanical counter display. The mechanical counter display may comprise a tape. The perforated dose counter chamber may therefore enable reliable washing of the inhaler, if desired by the user, and may therefore dry out without the display window misting up.

The dose counter chamber may be perforated by a drain hole formed through an outer hole of the body. The drain hole may be located at a bottom portion of the body of the inhaler, thereby enabling full draining of the inhaler to be encouraged after washing when the inhaler is brought into an upright position.

According to a further aspect of the present invention there is provided a dose counter for an inhaler, the dose counter having a display tape arranged to be incrementally driven from a tape stock bobbin onto an incremental tape take-up drive shaft, the bobbin having an internal bore supported by and for rotation about a support shaft, at least one of the bore and support shaft having a protrusion which is resiliently biased into frictional engagement with the other of the bore and support shaft with longitudinally extending mutual frictional interaction. This arrangement may provide good friction for the bobbin, thereby improving tape counter

display accuracy and preventing the bobbin from unwinding undesirably for example if the inhaler is accidentally dropped.

The support shaft may be forked and resilient for resiliently biasing the support shaft and bore into frictional engagement.

The support shaft may have two forks, or more in some cases, each having a radially extending protrusion having a friction edge extending therealong parallel to a longitudinal axis of the support shaft for frictionally engaging the bore of the support shaft with longitudinally extending frictional interaction therebetween.

The bore may be a smooth circularly cylindrical or substantially cylindrical bore.

Each of the above inhalers in accordance with aspects of the present invention may have a medicament canister mounted thereto.

The canister may comprise a pressurised metered dose canister having a reciprocally movable stem extending therefrom and movable into a main canister portion thereof for releasing a metered dose of medicament under pressure, for example by operating a metered dose valve inside the canister body. The canister may be operable by pressing by hand on the main canister body.

In cases in which one or more support rails or inner wall support formations are provided, the canister may at all times when within the canister chamber have a clearance of about 0.25 to 0.35 mm from the first inner wall support formation. The clearance may be almost exactly 0.3 mm. This clearance which may apply to the canister body itself or to the canister once a label has been applied, is enough to allow smooth motion of the canister in the inhaler while at the same time preventing substantial rocking of the canister which could result in inaccurate counting by a dose counter of the inhaler, especially when lower face of the canister is arranged to engage an actuator member of the dose counter for counting purposes.

According to a further aspect of the invention, a method of assembling a dose counter for an inhaler comprises the steps of providing a tape with dosing indicia thereon; providing tape positioning indicia on the tape; and stowing the tape while monitoring for the tape positioning indicia with a sensor. The method advantageously permits efficient and accurate stowing of the tape, e.g. by winding.

The dosing indicia may be provided as numbers, the tape positioning indicia may be provided as one or more lines across the tape. The stowing step comprises winding the tape onto a bobbin or shaft, and, optionally, stopping winding when the positioning indicia are in a predetermined position. The tape may be provided with pixelated indicia at a position spaced along the tape from the positioning indicia.

The tape may also be provided with a priming dot.

According to a further aspect of the invention, a tape system for a dose counter for an inhaler has a main elongate tape structure, and dosing indicia and tape positioning indicia located on the tape structure. The tape positioning indicia may comprise at least one line extending across the tape structure. The tape system may comprise pixelated indicia located on the tape structure and spaced from the positioning indicia. The tape system may comprise a priming dot located on the tape structure. The positioning indicia may be located between the timing dot and the pixelated indicia. The main elongate tape structure may have at least one end thereof wound on a bobbin or shaft.

A further aspect of the invention provides a method of designing an incremental dose counter for an inhaler comprising the steps of calculating nominal canister fire and dose counter positions for a dose counter actuator of the inhaler; calculating a failure/success rate for dose counters built to tolerance levels for counting each fire of inhalers in which the dose counter actuators may be applied; and selecting a tolerance level to result in said failure/success rate to be at or below/above a predetermined value. This is highly advantageous in that it allows an efficient and accurate prediction of the reliability of a series of inhaler counters made in accordance with the design.

The method of designing may include selecting the failure/success rate as a failure rate of no more than one in 50 million. The method of designing may include setting an average count position for dose counters built to the tolerances to be at or after an average fire position thereof during canister firing motion. The method of designing may include setting the average count position to be about 0.4 to 0.6 mm after the average fire position, such as about 0.48 mm after. The method of designing may include setting tolerances for the standard deviation of the fire position in dose counters built to the tolerances to be about 0.12 to 0.16 mm, such as about 0.141 mm. The method of designing may include setting tolerances for the standard deviation of the count positions in dose counters built to the tolerances to be about 0.07 to 0.09 mm, such as about 0.08 mm. A further aspect of the invention provides a computer implemented method of designing an incremental dose counter for an inhaler which includes the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing in a production run a series of incremental dose counters for inhalers which comprises manufacturing the series of dose counters in accordance with the aforementioned method of designing.

A further aspect of the invention provides a method of manufacturing a series of incremental dose counters for inhalers, which comprises manufacturing the dose counters with nominal canister fire and dose count positions of a dose counter actuator relative to a dose counter chassis (or inhaler main body), and which includes building the dose counters with the average dose count position in the series being, in canister fire process, at or after the average canister fire position in the series.

According to a further aspect of the invention, the method provides fitting each dose counter in the series of incremental dose counters to a corresponding main body of an inhaler.

These aspects advantageously provide for the production run of a series of inhalers and dose counters which count reliably in operation.

According to a further aspect of the invention, an incremental dose counter for a metered dose inhaler has a body arranged to retain a canister for movement of the canister relative thereto, the incremental dose counter having a main body, an actuator arranged to be driven and to drive an incremental output member in a count direction in response to canister motion, the actuator being configured to restrict motion of the output member in a direction opposite to the count direction. This advantageously enables an inhaler dose counter to keep a reliable count of remaining doses even if dropped or otherwise jolted.

The output member may comprise a ratchet wheel. The actuator may comprise a pawl and in which the ratchet wheel and pawl are arranged to permit only one-way ratcheting motion of the wheel relative to the pawl. The dose counter may include an anti-back drive member fixed to the main body. In a rest position of the dose counter, the ratchet wheel is capable of adopting a configuration in which a back surface of one tooth thereof engages the anti-back drive member and the pawl is spaced from an adjacent back

surface of another tooth of the ratchet wheel without positive drive/blocking engagement between the pawl and wheel.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention may be carried out in various ways and preferred embodiment of a dose counter, inhaler and methods of assembly, design and manufacture will now be described with reference to the accompanying drawings in which:

FIG. **1** is an isometric view of a main body of an embodiment of an inhaler related to the invention together with a mouthpiece cap therefor;

FIG. **2** is a top plan view of the components as shown in FIG. **1**;

FIG. **3**A is a section on the plane **3**A-**3**A in FIG. **2**;

FIG. **3**B is a view corresponding to FIG. **3**A but with a dose counter fitted to the main body of the inhaler;

FIG. **4**A is an exploded view of the inhaler main body, mouthpiece cap, dose counter and a dose counter window;

FIG. **4**B is a view in the direction **4**B in FIG. **4**C of a spring retainer of the dose counter;

FIG. **4**C is a top view of the spring retainer of FIG. **4**B;

FIG. **5** is a bottom view of the assembled inhaler main body, mouthpiece cap, dose counter and dose counter window;

FIGS. **6**A, **6**B, **6**C, **6**D, **6**E, **6**F, **6**G and **6**H are various views of dose counter components of the inhaler;

FIGS. **7**A and **7**B are sectional views showing canister clearance inside the main body of the inhaler;

FIG. **7**C is a further sectional view similar to that of FIG. **7**B but with the canister removed;

FIG. **7**D is a top plan view of the inhaler main body;

FIGS. **8**A, **8**B, **8**C and **8**D show the inhaler main body and dose counter components during assembly thereof;

FIG. **9** shows a sectional side view of a datum line for an actuator pawl of the dose counter;

FIGS. **10**A, **10**B, **10**C, **10**D, **10**E and **10**F show various side views of positions and configurations of the actuator pawl, a ratchet wheel, and a count pawl;

FIG. **11** shows distributions for tolerances of start, reset, fire, count and end positions for the actuator of the dose counter;

FIG. **12** is an enlarged version of part of FIG. **4**A;

FIG. **13** shows an end portion of a tape of the dose counter;

FIG. **14** shows a computer system for designing the dose counter;

FIG. **15** is an isometric view of a stock bobbin modified in accordance with the present invention for use in the dose counter of the inhaler of FIGS. **1** to **14**;

FIG. **16** shows an end view of the stock bobbin of FIG. **15**;

FIG. **17** is a section through a longitudinal axis of the stock bobbin of FIGS. **15** and **16**;

FIGS. **18**A, **18**B and **18**C are views of the stock bobbin of FIGS. **15** to **17** mounted in the dose counter chassis of FIGS. **1** to **14**, with the control elements of the forks of the second shaft (or split pin) having a profile slightly different to that in FIG. **6**F, with the forks in a compressed configuration;

FIGS. **19**A, **19**B and **19**C are views equivalent to FIGS. **18**A to **18**C but with the forks in a more expanded configuration due to a different rotational position of the stock bobbin;

FIG. **20** is an isometric view of the chassis assembled and including the stock bobbin of FIGS. **15** to **17** but excluding the tape for reasons of clarity;

FIG. **21** is a view of a preferred embodiment of a dry powder inhaler in accordance with the present invention;

FIG. **22** is an exploded view of the inhaler of FIG. **21**;

FIG. **23** is a view of a dose counter of the inhaler of FIG. **21**;

FIG. **24** is an exploded view of the dose counter shown in FIG. **23**;

FIG. **25** is an exploded view of parts of the inhaler of FIG. **21**; and

FIG. **26** is a view of a yoke of the inhaler of FIG. **21**.

DETAILED DESCRIPTION OF THE INVENTION

FIG. **1** shows a main body **10** of a manually operated metered dose inhaler **12** in accordance with an embodiment related to the present invention and having a mouthpiece cap **14** securable over a mouthpiece **16** of the main body.

The main body has a canister chamber **18** into which a canister **20** (FIG. **7**A) is slideable. The canister **20** has a generally cylindrical main side wall **24**, joined by a tapered section **26** to a head portion **28** having a substantially flat lower face **30** which has an outer annular drive surface **32** arranged to engage upon and drive an actuation pin **34** of a dose counter **36** as will be described. Extending centrally and axially from the lower face **30** is a valve stem **38** which is arranged to sealingly engage in a valve stem block **40** of the main body **10** of the inhaler **12**. The valve stem block **40** has a passageway **42** leading to a nozzle **44** for directing the contents of the canister **20**, namely active drug and propellant, towards an air outlet **46** of the inhaler main body **12**. It will be appreciated that due to gaps **48** between the canister **20** and an inner wall **50** of the main body **10** of the inhaler **12** an open top **52** of the main body **10** forms an air inlet into the inhaler **12** communicating via air passageway **54** with the air outlet **46**, such that canister contents exiting nozzle **44** mix with air being sucked by the user through the air passageway **54** in order to pass together through the air outlet and into the mouth of the user (not shown).

The dose counter **36** will now be described. The dose counter **36** includes an actuation pin **34** biased upwardly from underneath by a return spring **56** once installed in the main body **10**. As best shown in FIGS. **4**A, **6**H and **8**A, the pin **34** has side surfaces **58**, **60** arranged to slide between corresponding guide surfaces **62**, **64** located in a dose counter chamber **66** of the main body **10**, as well as an end stop surface **68** arranged to engage a corresponding end stop **70** formed in the dose counter chamber **66** to limit upward movement of the pin **34**. The pin **34** has a top part **72** which is circularly cylindrical and extends through an aperture **74** formed through a separator wall **76** which separates the canister chamber **18** from the dose counter chamber **66**. The top part **72** of the pin **34** has a flat top surface **78** which is arranged to engage the outer annular drive surface **32** of the canister **20**.

The actuation pin **34** is integrally formed with a drive or actuator pawl **80**. The actuator pawl **80** has a generally inverted U-shape configuration, having two mutually spaced and parallel arms **82**, **84** extending from a base portion of the actuation pin **34**, each holding at respective distal ends **88** thereof opposite ends of a pawl tooth member **90** which extends in a direction substantially perpendicular to the arms **82**, **84**, so as to provide what may be considered a "saddle" drive for pulling on each of the 11 drive teeth **92** of a ratchet wheel **94** of an incremental drive system **96** or ratchet mechanism **96** of the dose counter **36**. As shown for example in FIG. **10**B, the pawl tooth member **90** has a sharp lower

longitudinal side edge **98** arranged to engage the drive teeth **92**, the edge-to-surface contact provided by this engagement providing very accurate positioning of the actuator pawl **80** and resultant rotational positioning of the ratchet wheel **94**.

The dose counter **36** also has a chassis preassembly **100** which, as shown in FIGS. **4**A and **6**A, includes a chassis **102** having a first shaft **104** receiving the ratchet wheel **94** which is secured to a tape reel shaft **106**, and a second shaft (or split pin) **108** which is parallel to and spaced from the first shaft **104** and which slidably and rotationally receives a tape stock bobbin **110**.

As shown in FIG. **6**B, when the inhaler has not been used at all, the majority of a tape **112** is wound on the tape stock bobbin **110** and the tape **112** has a series of regularly spaced numbers **114** displayed therealong to indicate a number of remaining doses in the canister **20**. As the inhaler is repeatedly used, the ratchet wheel **94** is rotated by the actuator pawl **80** due to operation of the actuation pin **34** by the canister **20** and the tape **112** is incrementally and gradually wound on to the tape reel shaft **106** from the second shaft **108**. The tape **112** passes around a tape guide **116** of the chassis **102** enabling the numbers **114** to be displayed via a window **118** in a dose counter chamber cover **120** having a dose marker **132** formed or otherwise located thereon.

As shown in FIGS. **6**A and **6**D, the second shaft **108** is forked with two forks **124**, **126**. The forks **124**, **126** are biased away from one another. The forks have located thereon at diametrically opposed positions on the second shaft **108** friction or control elements **128**, **130**, one on each fork. Each control element extends longitudinally along its respective fork **124**, **126** and has a longitudinally extending friction surface **132**, **134** which extends substantially parallel to a longitudinal axis of the second shaft and is adapted to engage inside a substantially cylindrical bore **136** inside the tape stock bobbin **110**. This control arrangement provided between the bore **136** and the control elements **128**, **130** provides good rotational control for the tape stock bobbin **110** such that it does not unwind undesirably such as when the inhaler is dropped. The tape force required to unwind the tape stock bobbin **110** and overcome this friction force is approximately 0.1 N.

As can be seen in FIG. **6**D, as well as FIGS. **6**G and **10**A to **10**F, the chassis **102** is provided with an anti-back drive tooth **138** or count pawl **138** which is resiliently and substantially fixedly mounted thereto. As will be described below and as can be seen in FIGS. **10**A to **10**F, when the actuation pin **34** is depressed fully so as to fire the metered valve (not shown) inside the canister **20**, the actuator pawl **80** pulls down on one of the teeth **92** of the ratchet wheel **94** and rotates the wheel **94** anticlockwise as shown in FIG. **6**D so as to jump one tooth **92** past the count pawl **138**, thereby winding the tape **112** a distance incrementally relative to the dose marker **122** on the dose counter chamber **120** so as to indicate that one dose has been used.

With reference to FIG. **10**B, the teeth of the ratchet wheel **94** have tips **143** which are radiused with a 0.1 mm radius between the flat surfaces **140**, **142**. The ratchet wheel **94** has a central axis **145** which is 0.11 mm above datum plane **220** (FIG. **9**). A top/nose surface **147** of the anti-back drive tooth **138** is located 0.36 mm above the datum plane **220**. The distance vertically (i.e. transverse to datum plane **220**—FIG. **9**) between the top nose surface **147** of the anti-back drive tooth is 0.25 mm from the central axis **145** of the wheel **94**. Bump surface **144** has a lateral extent of 0.20 mm, with a vertical length of a flat **145'** thereof being 1 mm, the width of the bump surface being 1.22 mm (in the direction of the axis **145**), the top **149** of the bump surface **144** being 3.02 mm vertically below the axis **145**, and the flat **145'** being spaced a distance sideways (i.e. parallel to the datum plane **220**) 2.48 mm from the axis **145**. The top surface **78** of the pin **34** (FIG. **6**H) is 11.20 mm above the datum plane **220** (FIG. **9**) when the actuator pawl **80** and pin **34** are in the start configuration. The length of the valve stem **22** is 11.39 mm and the drive surface **32** of the canister **20** is 11.39 mm above the datum plane **220** when the canister is at rest waiting to be actuated, such that there is a clearance of 0.19 mm between the canister **20** and the pin **34** in this configuration.

FIGS. **10**A and **10**B show the actuator pawl **80** and ratchet wheel **94** and count pawl **138** in a start position in which the flat top **78** of the pin **34** has not yet been engaged by the outer annular drive surface **32** of the canister **20** or at least has not been pushed down during a canister depression.

In this "start" position, the count pawl **138** engages on a non-return back surface **140** of one of the teeth **92** of the ratchet wheel **94**. The lower side edge **98** of the actuator pawl is a distance "D" (FIG. **9**) 1.33 mm above datum plane **220** which passes through bottom surface or shoulder **41** of valve stem block **40**, the datum plane **220** being perpendicular to a main axis "X" of the main body **10** of the inhaler **12** which is coaxial with the centre of the valve stem block bore **43** and parallel to a direction of sliding of the canister **20** in the main body **10** of the inhaler **12** when the canister is fired.

As shown in FIG. **10**B, an advantageous feature of the construction is that the pawl tooth/actuator **90** acts as a supplementary anti-back drive member when the inhaler **12** is not being used for inhalation. In particular, if the inhaler **12** is accidentally dropped, resulting in a jolt to the dose counter **36** then, if the wheel **94** would try to rotate clockwise (backwards) as shown in FIG. **10**B, the back surface **140** of a tooth will engage and be blocked by the tooth member **90** of the pawl **80**. Therefore, even if the anti-back drive tooth **138** is temporarily bent or overcome by such a jolt, undesirable backwards rotation of the wheel **94** is prevented and, upon the next canister firing sequence, the pawl **90** will force the wheel **94** to catch up to its correct position so that the dose counter **36** continues to provide correct dosage indication.

FIG. **10**C shows a configuration in which the actuator pawl **80** has been depressed with the pin **34** by the canister **20** to a position in which the side edge **98** of the pawl tooth member **90** is just engaged with one of the teeth **92** and will therefore upon any further depression of the pin **34** begin to rotate the wheel **94**. This is referred to as a "Reset" position or configuration. In this configuration, the lower side edge **98** of the actuator **80** is 0.64 mm above the datum plane **220**.

FIG. **10**D shows a configuration in which the actuator pawl **80** has been moved to a position lower than that shown in FIG. **10**C and in which the metered dose valve (not shown) inside the canister has at this very position fired in order to eject active drug and propellant through the nozzle **44**. It will be noted that in this configuration the count pawl **138** is very slightly spaced from the back surface **140** of the same tooth **92** that it was engaging in the configuration of FIG. **10**D. The configuration shown in FIG. **10**D is known as a "Fire" configuration. In this configuration the lower side edge **98** of the actuator **80** is 0.47 min below the datum plane **220**.

FIG. **10**E shows a further step in the sequence, called a "Count" position in which the actuator pawl **80** has rotated the ratchet wheel **94** by the distance circumferentially angularly between two of the teeth **92**, such that the count pawl **138** has just finished riding along a forward surface **142** of one of the teeth **92** and has resiliently jumped over the tooth

into engagement with the back surface **140** of the next tooth. Accordingly, in this "Count" configuration, a sufficiently long stroke movement of the pin **34** has occurred that the tape **112** of the dose counter **36** will just have counted down one dose. In this configuration, the lower side edge **98** of the actuator is 0.95 mm below the datum plane **220**, Accordingly, in this position, the actuator **80** generally, including edge **98**, is 0.48 mm lower than in the fire configuration. It has been found that, although the count configuration happens further on than the fire configuration, counting is highly reliable, with less than 50 failed counts per million. This is at least partially due to momentum effects and to the canister releasing some back pressure on the user in some embodiments as its internal metering valve fires.

In the configuration of FIG. **10**F, the pawl **80** has been further depressed with the pin **34** by the canister **20** to a position in which it is just disengaging from one of the teeth **92** and the actuator pawl **80** is assisted in this disengagement by engagement of one of the arms **84** with a bump surface **144** on the chassis **102** (see FIG. **6**G) and it will be seen at this point of disengagement, which is called an "End" configuration, the count pawl **138** is positioned exactly halfway or substantially halfway between two of the drive teeth **92**. This advantageously means therefore that there is a minimum chance of any double counting or non-counting, which would be undesirable. In the end configuration, the side edge **98** of the actuator is 1.65 mm below the datum plane **220**. It will be appreciated that any further depression of the actuator pawl **80** and pin **34** past the "End" configuration shown in FIG. **10**F will have no effect on the position of the tape **112** displayed by the dose counter **36** since the actuator pawl **80** is disengaged from the ratchet wheel **94** when it is below the position shown in FIG. **10**F.

As shown in FIGS. **7**C and **7**D, the inner wall **50** of the main body **10** is provided with a two-step support rail **144** which extends longitudinally along inside the main body and is located directly adjacent the aperture **74**. As shown in FIG. **7**B a diametrically opposed two-step support rail **146** is also provided and this diametrically opposed in the sense that a vertical plane (not shown) can pass substantially directly through the first rail **144**, the aperture **74**, a central aperture **148** of the valve stem block **40** (in which canister stem **25** is located) and the second two-step support rail **146**. As shown in FIG. **7**A and schematically in FIG. **7**B, the rails **144, 146** provide a maximum clearance between the canister **20** and the rails **144, 146** in a radial direction of almost exactly 0.3 mm, about 0.25 to 0.35 mm being a typical range. This clearance in this plane means that the canister **20** can only rock backwards and forwards in this plane towards away from the actuation pin **34**. A relatively small distance and this therefore prevents the canister wobbling and changing the height of the actuation pin **34** *a* as to undesirably alter the accuracy of the dose counter **36**. This is therefore highly advantageous.

The inner wall **50** of the main body **10** is provided with two further two-step rails **150** as well as two pairs **152, 154** of rails extending different constant radial amounts inwardly from the inner wall **50**, so as to generally achieve a maximum clearance of almost exactly 0.3 mm around the canister **20** for all of the rails PH, **146, 150, 152, 154** spaced around the periphery of the inner wall **50**, in order to prevent undue rocking while still allowing canister motion freely inside the inhaler **12**. It will be clear from FIG. **7**C for example that the two-step rails have a first portion near an outlet end **156** of the canister chamber **18**, the first portion having a substantially constant radial or inwardly-extending width, a first step **160** leading to a second portion **162** of the rail, the second portion **102** having a lesser radial or inwardly extending extent than the first portion **156**, and finally a second step **164** at which the rail merges into the main inner wall **50** main surface.

A method of assembling the inhaler **12** will now be described.

With reference to FIG. **8**A, the main body **10** of the inhaler **12** is formed by two or more plastics mouldings which have been joined together to the configuration shown.

As shown in FIG. **8**B, the actuator pawl **80** and pin **34** are translated forward into position into a pin receiving area **166** in the dose counter chamber **66** and the pin **34** and actuator **80** may then be raised until the pin **34** emerges through the aperture **74**.

Next, the return spring **56** may be inserted below the pin **34** and a generally cylindrical annular lower end **168** of the spring **56** may be moved by a tweezer or tweezer-like assembly tool (not shown) into engagement with a shelf **170** of a spring retainer **172** in the dose counter chamber **66**. The spring retainer **172** is U-shaped and the shelf **170** is U-shaped and has a recess **174** formed below it. As shown in FIGS. **4**B, **4**C and **12** shelf **170** includes three chamfer surfaces **176, 178, 180** arranged to assist in moving the lower end of the spring **168** into position onto the shelf using the assembly tool (not shown). Once the lower end of the spring **168** is in place, the assembly tool (not shown) can easily be removed at least partly via the recess **174** below the lower end **168** of the spring **56**.

The tape **112** is attached at one end (not shown) to the tape stock bobbin **110** and is wound onto the bobbin by a motor **200** (FIG. **13**) having a hexagonal output shaft **202** which engages in a hexagonal socket **204** (FIG. **6**B) of the bobbin. During winding, the tape is monitored by a sensor **206**, which may be in the form of a camera or laser scanner, which feeds data to a computer controller **205** for the motor **200**. The controller **205** recognises three positioning markers **210** in the form of lines across the tape **112** and stops the motor **202** when the tape **112** is nearly fully wound onto the bobbin **110**, such that the distal end **212** of the tape **112** can be secured, e.g. by adhesive, to the tape reel shaft **106**. The controller **205** also recognises a pixelated tape size marker **214** observed by the sensor **206** and logs in a stocking system data store **217** details of the tape **112** such as the number of numbers **114** on the tape, such as one hundred and twenty or two hundred numbers **114**. Next, the tape reel shaft is wound until an appropriate position of the lines **210** at which a priming dot **216** will, once the bobbin **110** and reel shaft **106** are slid onto the second shaft **108** and second shaft **104**, be in a position to be located in the window **118** when the inhaler **12** is fully assembled. In the embodiments, the bobbin **110** and reel shaft **106** may be slid onto the shafts **108, 104** before the tape **112** is secured to the reel shaft **106** and the reel shaft may then be wound to position the priming dot **216**.

Next, the assembled dose counter components of the chassis preassembly **100** shown in FIG. **6**B may as shown in FIG. **8**C be inserted into the dose counter chamber **66**, with pins **182, 184, 186** formed on the main body **10** in the dose counter chamber **66** passing through apertures or slots **188, 190, 192** formed on the chassis **102**, such that the pins **182, 184, 186** extend through (or at least into) the apertures or slots **188, 190, 192**. With the chassis **102** being relatively firmly pushed towards the main body **10**, the pins **182, 184, 186** are then heat staked and the chassis **102** is therefore after this held very firmly in position in the main body and is unable to move, thereby assisting in providing great accuracy for the dose counter **36**. Next, as shown in FIG. **8**D, the

dose counter chamber cover **120** may be fitted over the dose counter chamber **66** and may be secured in place such as by welding, with the priming dot **216** being displayed through the window.

The user can, when readying the inhaler **12** for first use, prime the inhaler by depressing the canister **20** three times which will bring the first number **114** on the tape into display through the window **118** in place of the priming dot **216**, the number **114** shown in FIG. **8**D being "200", thereby indicating that 200 doses are remaining to be dispensed from the canister **20** and inhaler **12**.

As shown in FIG. **8**D, and in FIG. **5**, an open drain hole **194** is provided at the bottom of the dose counter chamber **66** by a substantially semi-circular cut-out or recess formation **196** in a lower surface **198** of the main body **10** of the inhaler. Accordingly, if the user (not shown) should decide to wash the main body **10** of the inhaler, for example after encountering an unhygienic situation or simply as a matter of choice, the drain hole **194** allows initial draining of water from inside the dose counter chamber **66** and also thereafter evaporation of water or any aqueous matter in the dose counter chamber **66** so that the window **118** does not mist up undesirably.

FIG. **14** shows a computer system **230** for designing the dose counter **36** and in particular for calculating distributions representative of average positions and standard deviations in a production series of inhalers of the start, reset, fire, count and end positions of the actuator lower side edge **98** relative to the datum plane **220** (FIG. **9**) and therefore of the actuator pawl **80** generally relative to the ratchet wheel **94**, chassis **102** and, when the inhaler **12** is fully assembled, the main body **10** of the inhaler **12**. The computer system **230** includes a data store **232**, a CPU **234**, an input device **236** (such as a keyboard or communication port) and an output device **238** (such as a communications port, display screen and/or printer). A user may enter data via the input device **236** which may be used by the CPU **234** in a mathematical calculation to predict count failure rates when the various dose counters are to be built in a series with dose counter positions set with given averages and standard deviations and taking into account any momentum/inertia effects and metering valve user-back-pressure reduction effect which will occur upon canister firing of a given type of canister. The computer system **230** is thus mathematically used to design the distributions. For the inhaler **12** described herein with the dose counter **36** and canister **20**, the distributions are designed as shown in FIG. **11**. The x axis shows distance of the lower side surface **98** of the actuator **80** above the datum plane **220** and the y axis is representative of the distribution. Thus, curve **240** shows that the start configuration has an average 1.33 mm above the datum plane **200** (standard deviation is 0.1 mm), curve **242** shows that the reset configuration has an average of 0.64 mm above the datum plane **220** (standard deviation is 0.082 mm), curve **244** shows the fire configuration has an average 0.47 mm below the datum plane **220** (standard deviation is 0.141 mm), curve **246** shows the count configuration has an average 0.95 mm below the datum plane **220** (standard deviation is 0.080 mm), and curve **248** shows the end configuration has an average of 1.65 mm below the datum plane **220** (standard deviation is 0.144 mm).

FIGS. **15** to **20** show a version of the inhaler modified in accordance with the present invention. In these drawings, the same reference numerals have been used to those in the earlier drawings to denote the equivalent components. The inhaler **12** is the same as that in FIGS. **1** to **14** apart from the following modifications.

First, it can be seen that there is a modification in that the drive teeth **92** of the ratchet wheel **94** have a different profile to that in FIGS. **1** to **14**. There are also only nine ratchet teeth **94** in this embodiment instead of eleven.

Additionally, as shown in FIGS. **18**C and **19**C, the control elements **128**, **130** on the forks **124**, **126** of the second shaft **108** have a tapered profile which is different to the profile of the control elements **128**, **130** shown in FIG. **6**F. Either profile can be used in the embodiment of FIGS. **15** to **20** however.

Furthermore, as shown in FIG. **15**, the tape stock bobbin **110** has an inwardly facing generally cylindrical engagement surface **300** with a wavelike form extending partially therealong. The engagement surface **300** has a cross-section **301** perpendicular to the longitudinal length of the stock bobbin **110** which is constant therealong. This cross-section **301** can be seen in FIG. **16** and consists of a series of ten regularly spaced concavities **302** and ten convex wall portions **304**. The convex wall portions **304** are equi-spaced between the concavities **302**. Each concavity **302** has a radius of 0.2 mm. Each convex wall portion **304** also has a radius of 0.2 mm. Finally, the cross section **301** also includes flat wall portions **306** between all of the radiused wall portions of the concavities **302** and convex wall portions **304**. The geometry of the cross-section **301** is therefore defined by the radii of the concavities **302** and convex wall portions **304**, the flat wall portions **306** and the fact that there are ten concavities **302** and convex wall portions **304**.

The minor diameter of the engagement surface **300**, i.e. between the tips of opposite convex wall portions **304**, is 2.46 mm. The major diameter of the engagement surface **300**, i.e. between the outermost portions of the concavities **302**, is 2.70 mm. The undeformed tip to tip maximum diameter of the forks **124**, **126** of the split pin (the second shaft) **108**, i.e. in the region of the maximum radio extent of the control elements **128**, **130**, is 3.1 millimetres and it will therefore be appreciated that the forks **124**, **126** are resiliently compressed once the stock bobbin **110** has been assembled onto the split pin **108** in all rotational configurations of the stock bobbin **110** relative to the split pin **108**. The minimum gap between the forks **124**, **126** in the plane of the cross sections of FIGS. **18**C and **19**C is 1 mm when the split pin **108** is in the undeformed, pre-inserted state. When the split pin **108** is at maximum compression, as shown in FIGS. **18**A to **18**C when the control elements **128**, **130** are shown to be engaged on top of the convex wall portions **304**, the gap **308** between the tips **310**, **312** of the forks **124**, **126** is 0.36 mm. On the other hand, when the split pin **108** is at minimum compression (once inserted into the stock bobbin) as shown in FIGS. **19**A to **19**C, when the control elements **128**, **130** rest in the concavities **302**, the gap between the tips **310**, **312** of the forks **124**, **126** is 0.6 mm. The control elements **128**, **130** are outwardly radiused with a radius also of 0.2 mm such that they can just rest on the concavities **302** with full surface contact (at least at an axial location on the split pin where the tapered control elements are at their maximum radial extent), without rattling in, locking onto or failing to fit in the concavities **302**. The radii of the control elements **128**, **130** is therefore preferably substantially the same as the radii of the concavities **302**

It will be appreciated that whereas FIGS. **18**B and **19**B are end views along the coaxial axis of the stock bobbin **110** and split pin **108**, FIGS. **18**A and **19**A are cross-sections. FIG. **19**A is a section on the plane A-A' in FIG. **19**C and FIG. **18**A is a section at the same plane, but of course with the stock bobbin **110** rotated relative to the split pin **108**.

As the inhaler **12** is used and the ratchet wheel **94** rotates in order to count used doses, the stock bobbin rotates incrementally through rotational positions in which rotation is resisted, i.e. due to increasing compression of the split pin **108** at such rotational positions, and rotational positions in which rotation is promoted, i.e. due to decreasing compression of the split pin **108** at such rotational positions and this may involve a click forward of the stock bobbin **110** to the next position equivalent to that in FIGS. **19**A to **19**C in which the control elements **128**, **130** of the split pin art located in the concavities **302**. This functionality firstly allows the stock bobbin to unwind during use as required, but also prevents the tape **112** from loosening during transit if the inhaler **12** is dropped, such as onto a hard surface. This is highly advantageous, since the tape **11** is prevented from moving to a position in which it will give an incorrect reading regarding the number of doses in the canister.

During compression and expansion of the forks in the radial direction between the two configurations shown in FIGS. **18**C and **19**C, the forks **124**, **126** rotate about a point **316** on the split pin where the forks **124**, **126** come together. This rotational action means that there is a camming action between the forks **124**, **126** and the engagement surface **300** without significant friction but, nevertheless, the resilient forces provided by the regulator formed by the engagement surface **300** and forks **124**, **126** are able to regulate unwinding of the tape such that it does not easily occur during transit or if the inhaler **12** is dropped. It has been found during testing that a force of 0.3 to 0.4 N needs to be applied to the tape **112** to overcome the regulator at the stock bobbin **110**. 0.32 N is achieved with the control elements **128** having the profile shown in FIG. **19**C and 0.38 N is achieved with the profile of the control elements **128** altered to be as shown as described with reference to FIG. 6F. These forces are substantially higher than the 0.1 N force mentioned above and undesirable movement of the tape is substantially avoided even if the inhaler is dropped onto a hard surface. The modified arrangement of FIGS. **15** to **20** does not provide this force "constantly" such that there is overall not an undesirably high friction of the tape **112** as it passes over the other components of the dose counter because, due to the incremental nature of the resilient forces at the regulator, the tape **112** can incrementally relax as it slides over the stationary chassis components.

Instead of having ten concavities **302** and convex wall portions **304**, other numbers may be used, such as 8 or 12. However, it is preferred to have an even number, especially since two control elements **128**, **130** are provided, so that all of the control elements **128**, **130** will expand and contract simultaneously. However, other arrangements are envisaged with 3 or more forks and the number of concavities/convex wall portions may be maintained as an integer divisible by the number of forks to maintain a system with simultaneous expansion/contraction. For example, the use of 9, 12 or 15 concavities/convex wall portions with 3 forks is envisaged.

Instead of having the engagement surface **300** on the inside of the stock bobbin **110**, it could be placed on the outside of the stock bobbin **110** so as to be engaged by flexible external legs/pawls or similar.

It will be noted that the regulator provided by the engagement surface **300** and forks **124**, **126** does not only allow rotation of the stock bobbin in one direction as is the case with the ratchet wheel **94**. Rotation in both directions is possible, i.e. forwards and backwards. This means that during assembly, the stock bobbin **110** can be wound backwards during or after fitting the bobbin **100**, shaft **106** and tape **112** onto the carriage **102**, if desired.

The stock bobbin **110** and the carriage **102** including the split pin **108** are both moulded of polypropylene material.

It will be seen from FIG. **16** that the cross-sectional shape **301** is not symmetrical within the hexagonal socket **204**. This has enabled the hexagonal socket **204** to be maintained at a useful size while still allowing the desired size and geometry of the cross section **301** to fit without interfering with the hexagonal shape of the hexagonal socket **204** and also permits moulding to work during manufacture.

As shown in FIG. **17**, the stock bobbin **110** has a series of four circumferential ribs **330** inside it and a spaced thereabout. These hold the stock bobbin **110** on the correct side of the mould tool during moulding.

FIGS. **21** and **22** show a preferred embodiment in accordance with the invention of an inhaler **510** for dispensing a dry-powdered medicament in metered doses for patient inhalation. The inhaler **510** is as disclosed in FIGS. **1** to **16** or EP-A-1330280, the contents of which are hereby fully incorporated herein by reference, but with the stock bobbin **110** and second shaft **108** of the dose counter **516** modified so as to be as in FIGS. **15** to **20** hereof. Thus, the dry powder inhaler **510** generally includes a housing **518**, and an assembly **512** received in the housing (see FIG. **21**). The housing **518** includes a case **520** having an open end **522** and a mouthpiece **524** (FIG. **25**) for patient inhalation, a cap **526** secured to and closing the open end **522** of the case **520**, and a cover **528** pivotally mounted to the case **520** for covering the mouthpiece **524**. As shown in FIG. **22**, the inhaler **510** also includes an actuation spring **569**, first yoke **566** with opening **572**, bellows **540** with crown **574**, a reservoir **514**, second yoke **568** with hopper **542** and dose counter **516** mounted thereto, and case **520** has transparent window **5130** thereon for viewing dose counter tape indicia **5128**. The dose metering system also includes two cams **570** mounted on the mouthpiece cover **528** and movable with the cover **528** between open and closed positions. The cams **570** each include an opening **580** for allowing outwardly extending hinges **582** of the case **520** to pass therethrough and be received in first recesses **584** of the cover **528**. The cams **570** also include bosses **586** extending outwardly and received in second recesses **588** of the cover **528**, such that the cover **528** pivots about the hinges **582** and the cams **570** move with the cover **528** about the hinges **582**. As described in EP-A-1330280, cams **570** act upon cam followers **578** to move second yoke **568** up and down and thereby operate dose counter by engagement of pawl **5138** on the second yoke **568** with teeth **5136**. Remaining components of the inhaler are provided as, and operate as described, in EP-A-1330280.

The dose counting system **516** therefore includes a ribbon or tape **5128** (FIGS. **23** & **24**), having successive numbers or other suitable indicia printed thereon, in alignment with a transparent window **5130** provided in the housing **18** (see FIG. **22**). The dose counting system **516** includes the rotatable stock bobbin **110** (as described above), an indexing spool **5134** rotatable in a single direction, and the ribbon **5128** rolled and received on the bobbin **110** and having a first end **5127** secured to the spool **5134**, wherein the ribbon **5128** unrolls from the bobbin **110** so that the indicia are successively displayed as the spool **5134** is rotated or advanced. In FIGS. **23** and **24** the wavelike engagement surface **300** of the bobbin **110** is not shown for the purposes of clarity.

The spool **134** is arranged to rotate upon movement of the yokes **566**, **568** to effect delivery of a dose of medicament from reservoir **514**, such that the number on the ribbon **5128** is advanced to indicate that another dose has been dispensed by the inhaler **510**. The ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase or

decrease upon rotation of the spool **5134**. For example, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, decrease upon rotation of the spool **5134** to indicate the number of doses remaining in the inhaler **510**. Alternatively, the ribbon **5128** can be arranged such that the numbers, or other suitable indicia, increase upon rotation of the spool **5134** to indicate the number of doses dispensed by the inhaler **10**.

The indexing spool **5134** includes radially extending teeth **5136**, which are engaged by pawl **5138** extending from a cam follower **578** of the second yoke **568** upon movement of the yoke to rotate, or advance, the indexing spool **5134**. More particularly, the pawl **5138** is shaped and arranged such that it engages the teeth **5136** and advances the indexing spool **5134** only upon the mouthpiece cover **528** being closed and the yokes **566**, **568** moved back towards the cap **526** of the housing **518**.

The dose counting system **516** also includes a chassis **5140** that secures the dose counting system to the hopper **542** and includes shafts **108**, **5144** for receiving the bobbin **110** and the indexing spool **5134**. As described above with reference to FIGS. **1** to **20**, the bobbin shaft **108** is forked and includes radially nubs **5146** for creating a resilient resistance to rotation of the bobbin **110** on the shaft **108** by engaging with the wavelike engagement surface **300** inside the bobbin **110**. A clutch spring **5148** is received on the end of the indexing spool **5134** and locked to the chassis **5140** to allow rotation of the spool **5134** in only a single direction.

Various modifications may be made to the embodiment shown without departing from the scope of the invention as defined by the accompanying claims as interpreted under patent law.

What is claimed is:

1. An incremental dose counter for a metered dose inhaler having a body arranged to retain a canister for movement of the canister relative thereto, the incremental dose counter having a main body, an actuator arranged to be driven and to drive an incremental output member in a count direction in response to canister motion, the actuator being configured to restrict motion of the output member in a direction opposite to the count direction, such that the actuator acts as an anti-back drive member when the actuator is in a non-depressed position, and wherein the incremental dose counter further comprises a second anti-back member configured to restrict motion of the output member in a direction opposite to the count direction when the actuator is disengaged from the output member by a bump surface.

2. The incremental dose counter as claimed in claim **1** in which the output member comprises a ratchet wheel.

3. The incremental dose counter as claimed in claim **2** in which the actuator comprises a pawl and in which the ratchet wheel and pawl are arranged to permit only one way ratcheting motion of the ratchet wheel relative to the pawl.

4. The incremental dose counter as claimed in claim **3** wherein the second anti-back member is fixed to the main body.

5. The incremental dose counter as claimed in claim **4** in which, when in a rest position of the dose counter, the ratchet wheel is capable of adopting a configuration in which a back surface of one tooth thereof engages the second anti-back member and the pawl is spaced from an adjacent back surface of another tooth of the ratchet wheel without positive drive/blocking engagement between the pawl and ratchet wheel.

6. A dose counter as claimed in claim **1** wherein an incremental counting system is arranged to move a counter display incrementally in a first direction from a first station to a second station in response to actuation input, wherein a regulator is provided which is arranged to act upon the counter display at the first station to regulate motion of the counter display at the first station to incremental movements.

* * * * *

EXHIBIT 5

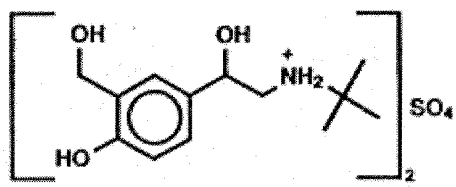
[TRADE NAME] HFA (ALBUTEROL SULFATE) INHALATION AEROSOL

For Oral Inhalation Only

PRESCRIBING INFORMATION

DESCRIPTION

The active ingredient of [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, a racemic salt, which is a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and has the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. [TRADE NAME] HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane) and ethanol.

Each actuation delivers 120 mcg albuterol sulfate, from the canister valve and 108 mcg albuterol sulfate, from the actuator mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister provides 200 inhalations. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three "test sprays" into the air, away from the face.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50% of total cardiac beta-adrenergic receptors. The precise

function of these receptors has not been established (**see WARNINGS for Cardiovascular Effects**.)

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical

Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 - 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 - 27 minutes in animals and 5 - 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. In a crossover study conducted in healthy male and female volunteers, high cumulative doses of [TRADE NAME] HFA Inhalation Aerosol (1,080 mcg of albuterol base administered over one hour) yielded mean peak plasma concentrations (C_{max}) and systemic exposure (AUC_{inf}) of approximately 4,100 pg/mL and 28,426 pg.hr/mL, respectively compared to approximately 3,900 pg/mL and 28,395 pg.hr/mL, respectively following the same dose of an active HFA-134a albuterol inhaler comparator. The terminal plasma half-life of albuterol delivered by [TRADE NAME] HFA Inhalation Aerosol was approximately 6 hours. Comparison of the pharmacokinetic parameters demonstrated no differences between the products.

No pharmacokinetic studies for [TRADE NAME] HFA Inhalation Aerosol have been conducted in neonates, children, or elderly subjects.

Clinical Trials

In a 6-week, randomized, evaluator-blind, placebo-controlled trial, [TRADE NAME] HFA Inhalation Aerosol (58 patients) was compared to an HFA-134a placebo inhaler (58 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. An active comparator HFA-134a albuterol inhaler arm (56 patients) was included.

Serial FEV_1 measurements, shown below as percent change from test-day baseline at Day 1 and at Day 43, demonstrated that two inhalations of [TRADE NAME] HFA Inhalation Aerosol produced significantly greater improvement in FEV_1 over the pre-treatment value than placebo, as well as a comparable bronchodilator effect to the active comparator HFA-134a albuterol inhaler.

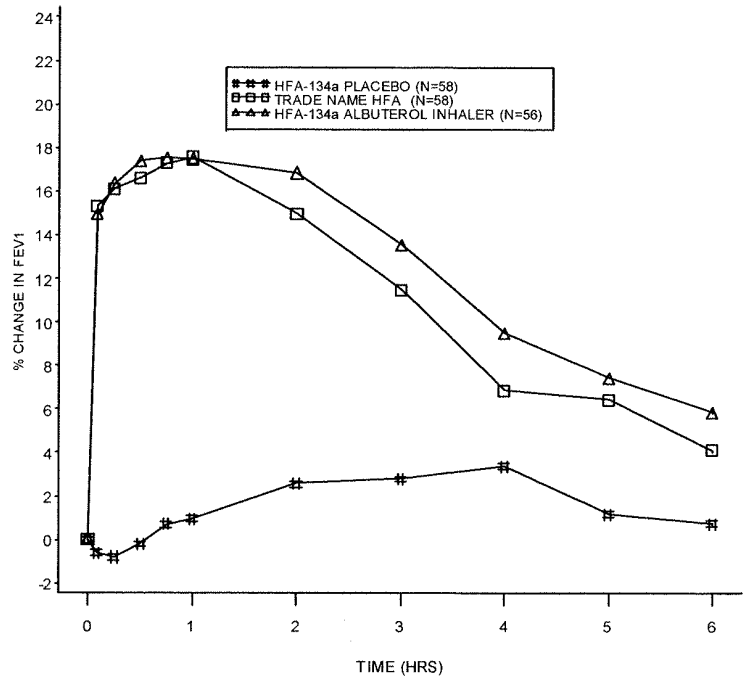
The mean time of onset of a 15% increase in FEV_1 at Day 1 was approximately 19 minutes and the mean time to peak effect was 70 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 over the pre-treatment value was approximately 3 hours. In some patients, the duration was as long as 6 hours.

In a placebo-controlled single-dose, crossover study in which [TRADE NAME] HFA Inhalation Aerosol, administered at albuterol doses of 90, 180 and 270 mcg, produced bronchodilator responses significantly greater than those observed with an HFA-134a placebo inhaler and comparable to an active comparator HFA-134a albuterol inhaler.

Some patients who participated in these clinical trials were using concomitant steroid therapy.

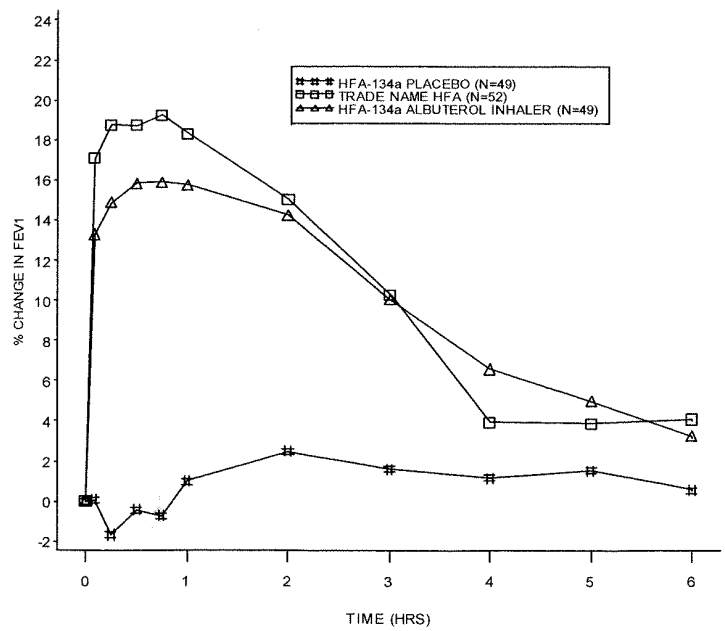
113 **FEV_1 as Mean Percent Change from Test-Day Pre-Dose in a**
114 **6-Week Clinical Trial**

115 **Day 1**



116

117 **Day 43**



INDICATIONS AND USAGE

[TRADE NAME] HFA Inhalation Aerosol is indicated in adults and children 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease.

CONTRAINDICATIONS

[TRADE NAME] HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other [TRADE NAME] HFA Inhalation Aerosol components.

WARNINGS

Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, [TRADE NAME] HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of [TRADE NAME] HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Use of Anti-inflammatory Agents: The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

Cardiovascular Effects: [TRADE NAME] HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of [TRADE NAME] HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, [TRADE NAME] HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

PRECAUTIONS

General

Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients See illustrated **Patient's Instructions for Use**. SHAKE WELL BEFORE USING. Patients should be given the following information:

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three "test sprays" into the air, away from the face.

KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The mouthpiece should be cleaned (with the canister removed) by running warm water through the top and bottom of the mouthpiece for 30 seconds at least once a week. The mouthpiece must be shaken to remove excess water, then air-dried thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to thoroughly air dry the mouthpiece.

If the mouthpiece should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing as described above.

If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, test spray twice away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly.

The action of [TRADE NAME] HFA Inhalation Aerosol lasts up to 4 to 6 hours. [TRADE NAME] HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of [TRADE NAME] HFA Inhalation Aerosol without consulting your physician. If you find that treatment with [TRADE NAME] HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, seek medical attention immediately. While you are taking [TRADE NAME] HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of [TRADE NAME] HFA Inhalation Aerosol.

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about use of [TRADE NAME] HFA Inhalation Aerosol. Effective and safe use of [TRADE NAME] HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use [TRADE NAME] HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta-Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as [TRADE NAME] HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: [TRADE NAME] HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 10 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at the low dose 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg

(approximately 630 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in Sprague-Dawley rats, the albuterol sulfate/HFA-134a formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of albuterol sulfate in pregnant women. [TRADE NAME] HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of [TRADE NAME] HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis: Albuterol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of [TRADE NAME] HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when albuterol sulfate is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of [TRADE NAME] HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics

The safety and effectiveness of [TRADE NAME] HFA Inhalation Aerosol in pediatric patients below the age of 12 years have not been established.

Geriatrics

Clinical studies of [TRADE NAME] HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

A total of 973 subjects were treated with [TRADE NAME] HFA Inhalation Aerosol during the worldwide clinical development program.

The adverse reaction information presented in the table below concerning [TRADE NAME] HFA Inhalation Aerosol is derived from a 6-week, evaluator-blind study which compared [TRADE NAME] HFA Inhalation Aerosol (180 mcg four times daily) with an HFA-134a placebo inhaler and an active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the [TRADE NAME] HFA Inhalation Aerosol treatment group and more frequently in the [TRADE NAME] HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse events reported for [TRADE NAME] HFA Inhalation Aerosol and the active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/ Adverse Event (as Preferred Term)		[TRADE NAME] Inhalation Aerosol (N = 58)	Active comparator HFA-134a Albuterol Inhaler (N = 56)	HFA-134a Placebo Inhaler (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the [TRADE NAME] HFA Inhalation Aerosol group and more frequently in the [TRADE NAME] HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the patients receiving [TRADE NAME] HFA Inhalation Aerosol but by a greater proportion of [TRADE NAME] HFA Inhalation Aerosol patients than placebo patients, which have the potential to be related to [TRADE NAME] HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection. Adverse events reported by 3% or more patients receiving [TRADE NAME] and by an equal or lesser proportion of [TRADE NAME] HFA Inhalation Aerosol patients than placebo patients included asthma, back pain, increased cough and infection (respiratory).

The most frequent adverse events occurring in three studies conducted in 32 volunteers or 25 asthmatics in which [TRADE NAME] HFA Inhalation Aerosol was administered as single cumulative albuterol doses of up to 1080 mcg over an hour (volunteers) or 1350 mcg over 1½ hours (asthmatics) were consistent with those associated with high-dose inhaled albuterol and included tremor, nervousness, and headache.

Rare cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of [TRADE NAME] HFA Inhalation Aerosol.

Treatment consists of discontinuation of [TRADE NAME] HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of [TRADE NAME] HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,300 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 2,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is

approximately 2,000 mg/kg (approximately 13,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 12 years and older is two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient.

Each actuation of [TRADE NAME] HFA Inhalation Aerosol delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the actuator mouthpiece. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than two weeks by releasing three "test sprays" into the air, away from the face.

If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

To maintain proper use of this product and to prevent medication build-up and blockage, it is important to keep the plastic mouthpiece clean. Wash the mouthpiece and air dry thoroughly at least once a week. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage. The inhaler may cease to deliver medication if not properly cleaned and air dried. See-**Information For Patients**.

HOW SUPPLIED [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a blue plastic actuator and dark blue dust cap each in boxes of one. Each canister contains 8.5 g of the formulation and provides 200 actuations (NDC 59310-179-20). Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

Rx only.

Store between 15° and 25°C (59° and 77°F). Avoid exposure to extreme heat and cold. For best results, canister should be at room temperature before use.

SHAKE WELL BEFORE USE.

The blue actuator supplied with [TRADE NAME] HFA Inhalation Aerosol should not be used with the canister from any other inhalation aerosol products. The [TRADE NAME] HFA Inhalation Aerosol canister should not be used with the actuator from any other inhalation aerosol products.

Once the labeled number of actuations (i.e. 200) has been used, the labeled amount of medication delivered from a canister cannot be assured. As a result, the inhaler should be discarded after 200 actuations, even though the canister may not be completely empty. Never immerse the canister into water to determine how full the canister is ("float test").

WARNING:
Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.

[TRADE NAME] HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

Manufactured by
IVAX Pharmaceuticals Ireland
Waterford, Republic of Ireland
for
IVAX Laboratories, Inc.
Miami, FL 33137 USA

Rev. 10/04B
########

TRADE NAME™ is a trademark of IVAX Research, Inc.

Attention Pharmacist:
Detach Patient's Instructions for use from package insert and dispense with the product.

TRADE NAME™ HFA

(albuterol sulfate)
Inhalation Aerosol

FOR ORAL INHALATION ONLY
Patient's Instructions For Use

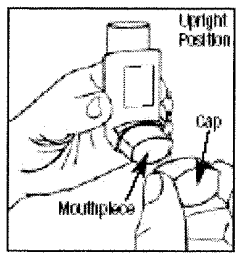


Fig. 1

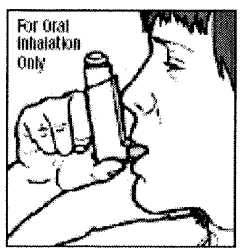


Fig. 2

Before using your [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use [TRADE NAME] HFA Inhalation Aerosol, under adult supervision, as instructed by the patient's doctor.

This inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant and is therefore CFC free.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.

2. As with all aerosol medications, it is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Prime by releasing three "test sprays" into the air, away from your face.

3. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into your mouth holding the inhaler in its upright position and closing your lips around it (see Figure 2). Make sure your tongue is placed below the mouthpiece.

4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS AND THEN IMMEDIATELY RELEASE THE TOP OF THE METAL CANISTER with your index finger (See Figure 2.)

5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

6. If your doctor has prescribed additional puffs, wait one minute, shake the inhaler again and repeat steps 3 through 5. Replace the cap after use.

7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE (CLOGGED). THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE PER WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

   Routine cleaning instructions: **Step 1**. Wash at least once a week. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds (see Figure A). **Never immerse the metal canister in water.**

Fig. A

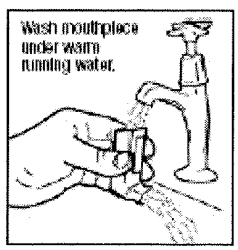


Fig. B

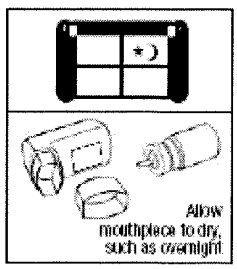
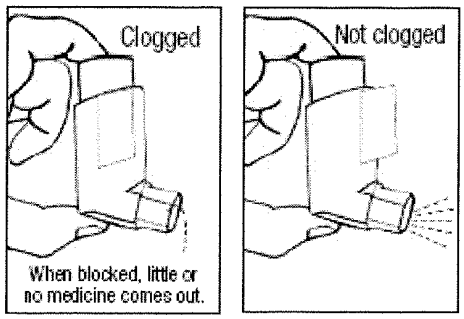


Fig. C



Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (see figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication build-up is more likely to occur if the mouthpiece is not allowed to air dry thoroughly.

IF YOUR INHALER BECOMES BLOCKED OR CLOGGED (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in Step 1 and air dry properly as described in Step 2.

IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE, OFF EXCESS WATER, replace the canister, and test spray twice into the air, away from your face, to remove most of the remaining water inside the mouthpiece. Then take your dose as prescribed. **After such use, rewash and air dry thoroughly as described in Steps 1 and 2.**

8. The inhaler should be discarded when the labeled number of actuations (i.e. 200) has been used. The labeled amount of medication in each inhalation cannot be assured after 200 actuations, even though the canister may not be completely empty. Before you reach the specific number of actuations, you should consult your doctor to determine whether a refill is needed. You should not take extra doses without consulting your doctor, neither should you stop using [TRADE NAME] HFA Inhalation Aerosol without consulting your doctor. Never immerse the canister into water to determine how full the canister is ("float test").

You may notice a slightly different taste or force to spray with [TRADE NAME] HFA Inhalation Aerosol, than you may be used to with other albuterol inhalation aerosol products.

DOSAGE:
Use only as directed by your doctor.

WARNINGS: The action of [TRADE NAME] HFA Inhalation Aerosol lasts up to 4 to 6 hours. Do not use more frequently than recommended. Do not increase the number of puffs or frequency of doses of [TRADE NAME] HFA Inhalation Aerosol without

consulting your doctor. If you find that treatment with [TRADE NAME] HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, seek medical attention immediately. While you are taking [TRADE NAME] HFA Inhalation Aerosol other inhaled drugs should be taken only as directed by your doctor. If you are pregnant or nursing, contact your doctor about the use of [TRADE NAME] HFA Inhalation Aerosol.

Common adverse effects of treatment with [TRADE NAME] HFA Inhalation Aerosol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of [TRADE NAME] HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use [TRADE NAME] HFA Inhalation Aerosol only with the blue actuator supplied with the product.

The [TRADE NAME] HFA Inhalation Aerosol actuator should not be used with the canister from other inhalation aerosol medications. The [TRADE NAME] HFA Inhalation Aerosol canister should not be used with the actuator from other inhalation aerosol medications.

Store between 15° and 25° C (59° and 77° F). Avoid exposure to extreme heat and cold. For best results, canister should be at room temperature.

Shake well before use.

Contents Under Pressure. Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your [TRADE NAME] HFA (albuterol sulfate) Inhalation Aerosol, does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

Manufactured by:
IVAX Pharmaceuticals Ireland
Waterford, Ireland

For:
IVAX Laboratories, Inc.
Miami FL 33137

[TRADE NAME] is a trademark of
IVAX Laboratories Inc.

Code #xxxxxx Rev. 10/04B

EXHIBIT 6

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROAIR HFA safely and effectively. See full prescribing information for PROAIR HFA Inhalation Aerosol

PROAIR HFA (albuterol sulfate) INHALATION AEROSOL
Initial U.S. Approval: 1981

----------RECENT MAJOR CHANGES----------
Dosage and Administration 03/12

----------INDICATIONS AND USAGE----------
PROAIR HFA Inhalation Aerosol is a beta$_2$-adrenergic agonist indicated for:
- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

----------DOSAGE AND ADMINISTRATION----------
For oral inhalation only
- Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, one inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise. (2.2)
- Priming information: Prime PROAIR HFA before using for the first time, or when the inhaler has not been used for more than 2 weeks. To prime PROAIR HFA, release 3 sprays into the air away from the face. Shake well before each spray. (2.3)
- Cleaning information: At least once a week, wash the actuator with warm water, shake off excess, and air dry thoroughly. (2.3)
- PROAIR HFA inhaler should be discarded when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation Aerosol: Each actuation delivers 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). Supplied in 8.5-g canister containing 200 actuations. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol Components. (4)

----------WARNINGS AND PRECAUTIONS----------
- Life-threatening paradoxical bronchospasm may occur. Discontinue PROAIR HFA immediately and treat with alternative therapy. (5.1)
- Need for more doses of PROAIR HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- PROAIR HFA is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders. (5.4, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue PROAIR HFA immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥3.0% and >placebo) are headache, tachycardia, pain, dizziness, pharyngitis, and rhinitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Other short-acting sympathomimetic aerosol bronchodilators and adrenergic drugs: May potentiate effect. (7)
- Beta-blockers: May decrease effectiveness of PROAIR HFA and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics, or non-potassium sparing diuretics: May potentiate hypokalemia or ECG changes. Consider monitoring potassium levels. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants: May potentiate effect of albuterol on the cardiovascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/12

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Bronchospasm

For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the usual dosage for adults and children 4 years and older is two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient.

2.2 Exercise-Induced Bronchospasm

The usual dosage for adults and children 4 years of age or older is two inhalations 15 to 30 minutes before exercise.

2.3 Administration Information

Administer PROAIR HFA by oral inhalation only. Shake well before each spray. To maintain proper use of this product and to prevent medication build-up and blockage, it is important to follow the cleaning directions carefully.

Priming: Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

Cleaning: As with all HFA-containing albuterol inhalers, to maintain proper use of this product and to prevent medication build-up and blockage, it is important to clean the plastic mouthpiece regularly. The inhaler may cease to deliver medication if the plastic actuator mouthpiece is not properly cleaned and dried. To clean: Wash the plastic mouthpiece with warm running water for 30 seconds, shake off excess water, and air dry thoroughly at least once a week**. If the patient has more than one PROAIR HFA inhaler, the patient should wash each one separately to prevent attaching the wrong canister to the wrong plastic actuator. In this way, the patient can be sure to always know the correct number of remaining doses. Never attach a canister of medication from any other inhaler to the PROAIR HFA actuator and never attach the PROAIR HFA canister to an actuator from any other inhaler.** If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage. If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, spray twice into the air away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly. *[see FDA-Approved Patient Labeling (17.9)]*.

Dose Counter: PROAIR HFA has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 3 times, at which point the number 200 will be displayed. The dose counter will count down each time a spray is released. When the dose counter reaches 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. PROAIR HFA inhaler should be discarded when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

3 DOSAGE FORMS & STRENGTHS

PROAIR HFA is an inhalation aerosol. PROAIR HFA is supplied as an 8.5 g/200 actuations pressurized aluminum canister with a red plastic actuator with a dose counter and white dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate *[see Warnings and Precautions (5.6)]*.

5 WARNINGS & PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical

evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

5.7 Coexisting Conditions

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR HFA may be associated with the following:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

A total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult and Adolescents 12 Years of Age and Older: The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/ Adverse Event (as Preferred Term)		PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0

Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Pediatric Patients 4 to 11 Years of Age: Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROAIR HFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m^2 basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD *[see Nonclinical Toxicology (13.2)]*.

8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

8.3 Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for the treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, and one single-dose crossover study comparing doses of 90, 180, and 270 mcg with placebo in 58 patients *[see Clinical Studies (14.1)]*. The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 24 adults and adolescents with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see Clinical Studies (14.2)].*

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo. The effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 55 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo *[see Clinical Studies (14.1)].*

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5.4, 5.7)]*.

All $beta_2$-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

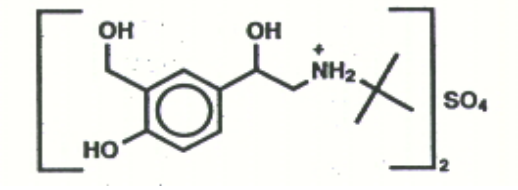
Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol.

Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3,200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

11 DESCRIPTION

The active ingredient of PROAIR HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, a racemic salt, of albuterol. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and has the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol. Albuterol sulfate is the official generic name in the United States, and salbutamol sulfate is the World Health Organization recommended generic name. PROAIR HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit with a dose counter. PROAIR HFA is for oral inhalation only. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane) and ethanol.

Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face. After priming, each actuation delivers 108 mcg albuterol sulfate, from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). Each canister provides 200 actuations (inhalations).

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albuterol sulfate is a $beta_2$-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of $beta_2$-adrenergic receptors on airway smooth muscle. Activation of $beta_2$-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium

concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac $beta_2$-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes *[see Warnings and Precautions (5.4)]*.

12.2 Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. In a crossover study conducted in healthy male and female volunteers, high cumulative doses of PROAIR HFA Inhalation Aerosol (1,080 mcg of albuterol base administered over one hour) yielded mean peak plasma concentrations (C_{max}) and systemic exposure (AUC_{inf}) of approximately 4,100 pg/mL and 28,426 pg/mL*hr, respectively compared to approximately 3,900 pg/mL and 28,395 pg/mL*hr, respectively following the same dose of an active HFA-134a albuterol inhaler comparator. The terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was approximately 6 hours. Comparison of the pharmacokinetic parameters demonstrated no differences between the products.

The pharmacokinetic profile of PROAIR HFA Inhalation Aerosol was evaluated in a two-way cross-over study in 11 healthy pediatric volunteers, 4 to 11 years of age. A single dose administration of PROAIR HFA Inhalation Aerosol (180 mcg albuterol base) yielded a least square mean (SE) C_{max} and $AUC_{0-\infty}$ of 1,100 (1.18) pg/mL and 5,120 (1.15) pg/mL*hr, respectively. The least square mean (SE) terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was 166 (7.8) minutes.

Metabolism and Elimination: Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Geriatric, Pediatric, Hepatic/Renal Impairment: No pharmacokinetic studies for PROAIR HFA Inhalation Aerosol have been conducted in neonates or elderly subjects.

The effect of hepatic impairment on the pharmacokinetics of PROAIR HFA Inhalation Aerosol has not been evaluated.

The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of

PROAIR HFA Inhalation Aerosol to patients with renal impairment *[see Use in Specific Populations (8.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 740 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 100 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 - 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 - 27 minutes in animals and 5 - 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Reproductive Toxicology Studies: A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on

a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at 50 mg/kg (approximately 630 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in Sprague-Dawley rats, the albuterol sulfate/HFA-134a did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 65 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

14 CLINICAL STUDIES

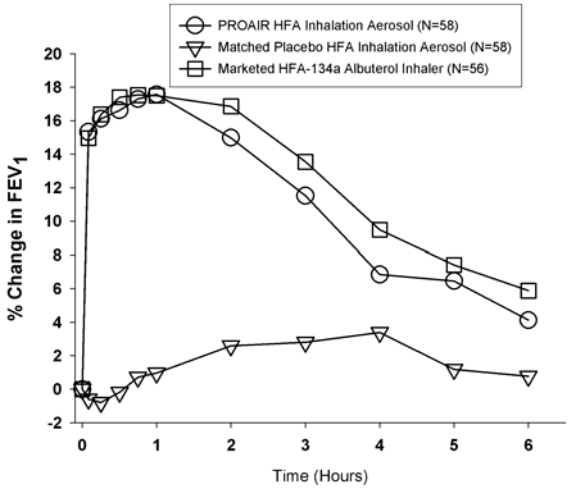
14.1 Bronchospasm Associated with Asthma

Adult and Adolescent Patients 12 Years of Age and Older: In a 6-week, randomized, double-blind, placebo-controlled trial, PROAIR HFA Inhalation Aerosol (58 patients) was compared to a matched placebo HFA inhalation aerosol (58 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol four times daily. An evaluator-blind marketed active comparator HFA-134a albuterol inhaler arm (56 patients) was included.

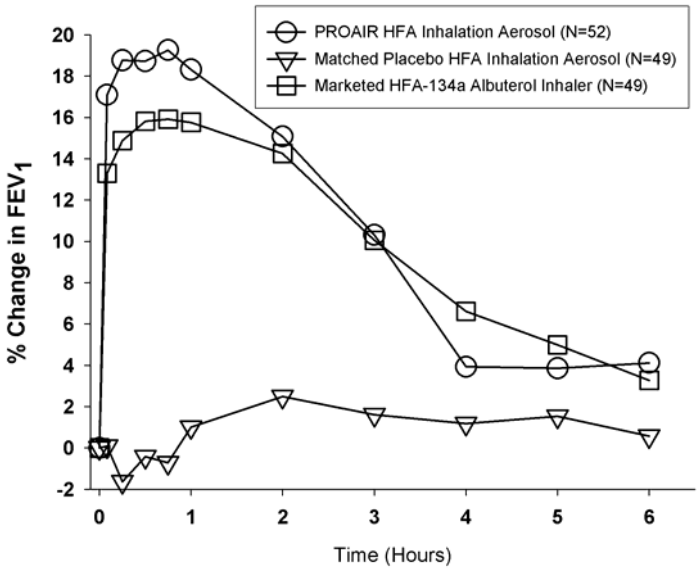
Serial FEV$_1$ measurements, shown below as percent change from test-day baseline at Day 1 and at Day 43, demonstrated that two inhalations of PROAIR HFA Inhalation Aerosol produced significantly greater improvement in FEV$_1$ over the pre-treatment value than the matched placebo, as well as a comparable bronchodilator effect to the marketed active comparator HFA-134a albuterol inhaler.

FEV$_1$ as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

Day 1



Day 43



In this study, 31 of 58 patients treated with PROAIR HFA Inhalation Aerosol achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect, and median duration of effect were 8.2 minutes, 47 minutes, and approximately 3 hours, respectively. In some patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study, PROAIR HFA Inhalation Aerosol, administered at albuterol doses of 90, 180 and 270 mcg, produced bronchodilator responses significantly greater than those observed with a matched placebo HFA inhalation aerosol and comparable to a marketed active comparator HFA-134a albuterol inhaler.

Pediatric Patients 4 to 11 Years of Age: In a 3-week, randomized, double-blind, placebo-controlled trial, the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (50 patients) was compared to a matched placebo HFA inhalation aerosol (45 patients) in asthmatic children 4 to 11 years of age at a dose of 180 mcg albuterol four times daily. Serial FEV_1 measurements, expressed as the maximum percent change from test-day baseline in percent predicted FEV_1 at Day 1 and at Day 22 observed within two hours post-dose, demonstrated that two inhalations of HFA albuterol sulfate produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo.

In this study, 21 of 50 pediatric patients treated with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect and median duration of effect were 10 minutes, 31 minutes, and approximately 4 hours, respectively. In some pediatric patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study in 55 pediatric patients 4 to 11 years of age, PROAIR HFA Inhalation Aerosol, administered at albuterol doses of 90 and 180 mcg, was compared with a matched placebo HFA inhalation aerosol. Serial FEV_1 measurements, expressed as the baseline-adjusted percent predicted FEV_1 observed over 6 hours post-dose, demonstrated that one and two inhalations of PROAIR HFA Inhalation Aerosol produced significantly greater bronchodilator responses than the matched placebo.

14.2 Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 24 adults and adolescents with exercise-induced bronchospasm (EIB), two inhalations of PROAIR HFA taken 30 minutes

before exercise prevented EIB for the hour following exercise (defined as maintenance of FEV_1 within 80% of post-dose, pre-exercise baseline values) in 83% (20 of 24) of patients as compared to 25% (6 of 24) of patients when they received placebo.

Some patients who participated in these clinical trials were using concomitant steroid therapy.

16 HOW SUPPLIED/STORAGE & HANDLING

PROAIR HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a red plastic actuator with a dose counter and white dust cap each in boxes of one. Each canister contains 8.5 g of the formulation and provides 200 actuations (NDC 59310-579-22). Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

SHAKE WELL BEFORE USE. Store between 15° and 25°C (59° and 77°F). Contents under pressure. Do not puncture or incinerate. Protect from freezing temperatures and prolonged exposure to direct sunlight. Exposure to temperatures above 120°F may cause bursting. For best results, canister should be at room temperature before use. Avoid spraying in eyes. Keep out of reach of children.

See FDA-Approved Patient Labeling (17.9) for priming and cleaning instructions.

The red actuator supplied with PROAIR HFA Inhalation Aerosol should not be used with the canister from any other inhalation aerosol products. The PROAIR HFA Inhalation Aerosol canister should not be used with the actuator from any other inhalation aerosol products.

PROAIR HFA inhaler has a dose counter attached to the actuator. Patients should never try to alter the numbers for the dose counter or tamper with the pin mechanism inside the actuator. Discard the PROAIR HFA inhaler when the counter displays 0 or after the expiration date on the product, whichever comes first. The labeled amount of medication in each actuation cannot be assured after the counter displays 0, even though the canister is not completely empty and will continue to operate. Never immerse the canister into water to determine how full the canister is ("float test").

PROAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.9)

Patients should be given the following information:

17.1 Frequency of Use

The action of PROAIR HFA Inhalation Aerosol should last for 4 to 6 hours. Do not use PROAIR HFA Inhalation Aerosol more frequently than recommended. Instruct patients to not increase the dose or frequency of doses of PROAIR HFA Inhalation Aerosol without consulting the physician. If patients find that treatment with PROAIR HFA Inhalation Aerosol becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately.

17.2 Priming and Cleaning

Priming: Priming is essential to ensure appropriate albuterol content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

Cleaning: To ensure proper dosing and prevent actuator orifice blockage, instruct patients to wash the red plastic actuator mouthpiece and dry thoroughly at least once a week. Instruct patients that if they have more than one PROAIR HFA inhaler, they should wash each one at separate times to prevent attaching the wrong canister to the wrong plastic actuator. In

this way, they can be sure they will always know the correct number of remaining doses. Patients should be instructed to never attach a canister of medicine from any other inhaler to the PROAIR HFA actuator and never attach the PROAIR HFA canister to an actuator from any other inhaler. Patients should not remove the canister from the actuator except during cleaning because reattachment may release a dose into the air and the dose counter will count down each time a spray is released. Detailed cleaning instructions are included in the illustrated Information for the Patient leaflet.

17.3 Dose Counter

Patients should be informed that PROAIR HFA has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 3 times, at which point the number 200 will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of two (e.g., 200, 198, 196, etc). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Patients should be informed to discard PROAIR HFA inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

17.4 Paradoxical Bronchospasm

Inform patients that PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm. Instruct patients to discontinue PROAIR HFA Inhalation Aerosol if paradoxical bronchospasm occurs.

17.5 Concomitant Drug Use

While patients are taking PROAIR HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by a physician.

17.6 Common Adverse Events

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.7 Pregnancy

Patients who are pregnant or nursing should contact their physician about the use of PROAIR HFA Inhalation Aerosol.

17.8 General Information on Use

Effective and safe use of PROAIR HFA Inhalation Aerosol includes an understanding of the way that it should be administered.

Shake well before each spray.

Use PROAIR HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the PROAIR HFA inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. Never immerse the canister in water to determine how full the canister is (“float test”).

In general, the technique for administering PROAIR HFA Inhalation Aerosol to children is similar to that for adults. Children should use PROAIR HFA Inhalation Aerosol under adult supervision, as instructed by the patient’s physician**.**

17.9 FDA-Approved Patient Labeling

See tear-off illustrated Information for the Patient leaflet.

U.S. Patent Nos. 5605674, 7105152, 7566445, 6446627

Mktd by: Teva Respiratory, LLC

Horsham, PA 19044

Mfd by: IVAX Pharmaceuticals Ireland
Waterford, Ireland

PROAIR® is a registered trademark of Teva Respiratory, LLC

Manufactured In Ireland PE 2444 03/12

Patient Information

PROAIR® HFA *(prō′ ār)*
(albuterol sulfate)
Inhalation Aerosol

Read this Patient Information before you start using PROAIR HFA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is PROAIR HFA?

PROAIR HFA is a prescription medicine used in people 4 years of age and older to:

- treat or prevent bronchospasm in people who have reversible obstructive airway disease
- prevent exercise induced bronchospasm

It is not known if PROAIR HFA is safe and effective in children under 4 years of age.

Who should not use PROAIR HFA?

Do not use PROAIR HFA if you are allergic to albuterol sulfate or any of the ingredients in PROAIR HFA. See the end of this leaflet for a complete list of ingredients in PROAIR HFA.

What should I tell my doctor before I use PROAIR HFA?

Before you use PROAIR HFA, tell your doctor if you:

- have heart problems
- have high blood pressure (hypertension)
- have convulsions (seizures)
- have thyroid problems
- have diabetes
- have low potassium levels in your blood
- are pregnant or plan to become pregnant. It is not known if PROAIR HFA will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if PROAIR HFA passes into your breast milk. Talk to your doctor about the best way to feed your baby if you are using PROAIR HFA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

PROAIR HFA and other medicines may affect each other and cause side effects. PROAIR HFA may affect the way other medicines work, and other medicines may affect the way PROAIR HFA works.

Especially tell your doctor if you take:

- other inhaled medicines or asthma medicines
- beta blocker medicines
- diuretics
- digoxin
- monoamine oxidase inhibitors
- tricyclic antidepressants

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use PROAIR HFA?

- For detailed instructions, see "**Instructions for Use**" at the end of this Patient Information.
- Use PROAIR HFA exactly as your doctor tells you to use it.
- If your child needs to use PROAIR HFA, watch your child closely to make sure your child uses the inhaler correctly. Your doctor will show you how your child should use PROAIR HFA.
- Each dose of PROAIR HFA should last up to 4 hours to 6 hours.
- **Do not** increase your dose or take extra doses of PROAIR HFA without first talking to your doctor.
- Get medical help right away if PROAIR HFA no longer helps your symptoms.
- Get medical help right away if your symptoms get worse or if you need to use your inhaler more often.
- While you are using PROAIR HFA, **do not** use other inhaled rescue medicines and asthma medicines unless your doctor tells you to do so.
- Call your doctor if your asthma symptoms like wheezing and trouble breathing become worse over a few hours or days. Your doctor may need to give you another medicine (for example, corticosteroids) to treat your symptoms.

What are the possible side effects of PROAIR HFA?

PROAIR HFA may cause serious side effects, including:

- **worsening trouble breathing, coughing and wheezing (paradoxical bronchospasm).** If this happens stop using PROAIR HFA and call your doctor or get emergency help right away. Paradoxical bronchospasm is more likely to happen with your first use of a new canister of medicine.
- **heart problems including faster heart rate and higher blood pressure**
- **possible death in people with asthma who use too much PROAIR HFA**

- **allergic reactions.** Call your doctor right away if you have the following symptoms of an allergic reaction:
  - itchy skin
  - swelling beneath your skin or in your throat
  - rash
  - worsening trouble breathing
- **low potassium levels in your blood**
- **worsening of other medical problems in people who also use PROAIR HFA including increases in blood sugar**

The most common side effects of PROAIR HFA include:

- your heart feels like it is pounding or racing (palpitations)
- chest pain
- fast heart rate
- shakiness
- nervousness
- headache
- dizziness
- sore throat
- runny nose

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PROAIR HFA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROAIR HFA?

- Store PROAIR HFA at room temperature between 59º F and 77º F (15º C and 25º C).
- Avoid exposure to extreme heat and cold.
- Shake the PROAIR HFA canister well before use.
- **Do not** puncture the PROAIR HFA canister.
- **Do not** store the PROAIR HFA canister near heat or a flame. Temperatures above 120° F may cause the canister to burst.
- **Do not** throw the PROAIR HFA canister into a fire or an incinerator.
- Avoid spraying PROAIR HFA in your eyes.

Keep PROAIR HFA and all medicines out of the reach of children.

General Information about the safe and effective use of PROAIR HFA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROAIR HFA for a condition for which it was not prescribed. Do not give PROAIR HFA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about PROAIR HFA. If you would like more information, talk with your doctor. You can ask your

pharmacist or doctor for information about PROAIR HFA that is written for health professionals.

For more information, go to www.ProAirHFA.com or call 1-888-482-9522.

What are the ingredients in PROAIR HFA?

Active ingredient: albuterol sulfate
Inactive ingredients: propellant HFA-134a and ethanol.

Instructions for Use

PROAIR® HFA *(prō′ ār)*
(albuterol sulfate)
Inhalation Aerosol

Read this Instructions for Use before you start using PROAIR HFA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

The Parts of Your PROAIR HFA Inhaler Device:

There are 2 main parts of your PROAIR HFA inhaler device including a:

- red plastic actuator that sprays the medicine from the canister. See Figure A.
- protective dust cap that covers the mouthpiece of the actuator. See Figure A.

There is also a metal canister that holds the medicine. See Figure A.

There is also a dose counter attached to the back of the actuator with a viewing window that shows you how many sprays of medicine you have left. See Figure B.

You will see a black dot in the viewing window on the actuator until the device has been primed 3 times. See Figure B and "**Priming Your PROAIR HFA Device**" below.

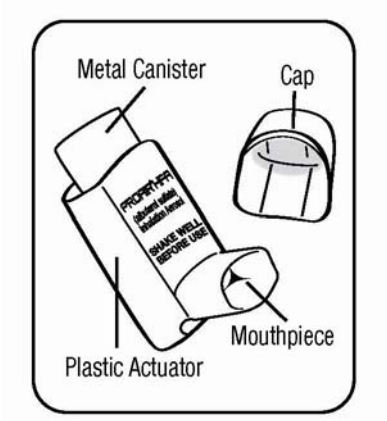


Figure A

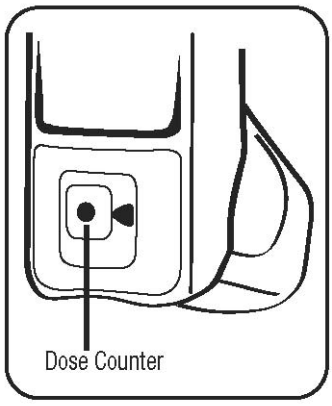


Figure B

- **Do not** use the PROAIR HFA actuator with a canister of medicine from any other inhaler.
- **Do not** use a PROAIR HFA canister with an actuator from any other inhaler, including another PROAIR HFA inhaler.

Priming Your PROAIR HFA Device:

Your PROAIR device must be primed before you use it for the first time or if your device has not been used for more than 14 days in a row. **Do not** prime your PROAIR HFA device every day.

- Remove your PROAIR HFA device from its package.
- Remove the protective dust cap from the mouthpiece.
- Shake the inhaler well, and spray it into the air away from your face. See Figure C.

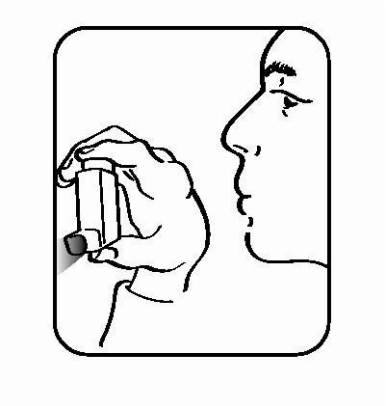


Figure C

- Shake and spray the inhaler like this 2 more times to finish priming it. The dose counter on the actuator should display the number 200 after you prime the actuator for the first time. See Figure D.

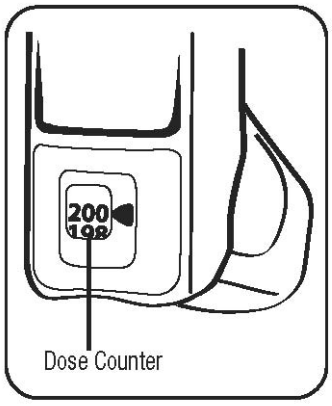


Figure D

Each Time You Use Your PROAIR HFA Device:

- Make sure the canister fits firmly in the plastic actuator.
- Look into the mouthpiece to make sure there are no foreign objects there, especially if the cap has not been used to cover the mouthpiece.

Reading the Dose Counter on Your PROAIR HFA Actuator

- The dose counter will count down each time a spray is released. The dose counter window shows the number of sprays left in your inhaler in units of 2

sprays. For example, there are 190 sprays left if the arrow is exactly opposite the number 190, or 189 sprays left if the arrow points between 190 and 188. See Figure D.

- When the dose counter reaches **0**, it will continue to show **0** and you should replace your PROAIR HFA device.
- The dose counter cannot be reset and is permanently attached to the actuator. **Never** change the numbers for the dose counter or touch the pin inside the actuator.
- **Do not** remove the canister from the plastic actuator except during cleaning. Reattaching the canister to the actuator may accidently release a dose of PROAIR HFA into the air. The dose counter will count down each time a spray is released.

Using Your PROAIR HFA Device:

Step 1. **Shake the inhaler well** before each spray. Take the cap off the mouthpiece of the actuator.

Step 2. Hold the inhaler with the mouthpiece down. See Figure E.

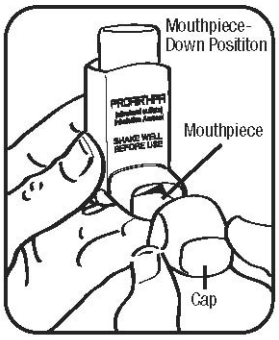


Figure E

Step 3. **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it. See Figure F.

Step 4. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth**. See Figure F.

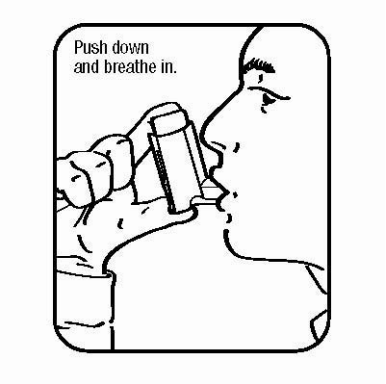


Figure F

Step 5. Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

Step 6. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

If your doctor has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure the cap snaps firmly into place.

Cleaning Your PROAIR HFA Device:

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. See Figure G and Figure H.

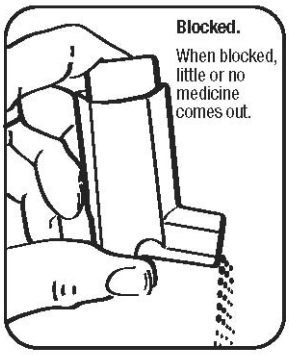


Figure G

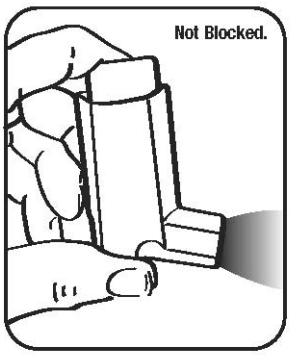


Figure H

- **Do not try to clean the metal canister or let it get wet.** The inhaler may stop spraying if it is not cleaned correctly.

- If you have more than 1 PROAIR HFA inhaler, wash each device at separate times to prevent putting the wrong canister together with the wrong plastic actuator. This way you can be sure you will always know the correct number of remaining doses of PROAIR HFA.
- **Wash the actuator** at least 1 time each week as follows**:**
  - Take the canister out of the actuator, and take the cap off the mouthpiece.
  - Hold the actuator under the faucet and run warm water through it for about 30 seconds. See Figure I.

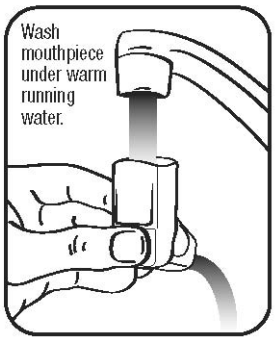


Figure I

  - Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. See Figure J.

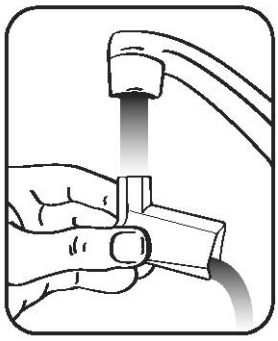


Figure J

  - Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat the washing instructions.
  - Let the actuator air-dry completely, such as overnight. See Figure K.

Figure K

- When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it twice into the air away from your face. Put the cap back on the mouthpiece.

If you need to use your inhaler before the actuator is completely dry:

- Shake as much water off the actuator as you can.
- Put the canister in the actuator and make sure it fits firmly.
- Shake the inhaler well and spray it twice into the air away from your face.
- Take your PROAIR HFA dose as prescribed.
- Follow the Cleaning Instructions above.

Replacing Your PROAIR HFA Device

- **When the dose counter on the actuator says the number 20,** the color of the numbers will change to red. The red numbers are to remind you to refill your prescription or ask your doctor for another prescription for PROAIR HFA. When the dose counter reaches **0**, the background color will change to solid red.
- **Throw the PROAIR HFA inhaler away** as soon as the dose counter says **0** or after the expiration date on the PROAIR HFA packaging, whichever comes first. You should not keep using the inhaler after 200 sprays even though the canister may not be completely empty. You cannot be sure you will receive any medicine after using 200 sprays.
- **Do not use the inhaler** after the expiration date on the PROAIR HFA packaging.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Marketed by Teva Respiratory, LLC
Horsham, PA 19044

Manufactured by IVAX Pharmaceuticals Ireland

Waterford, Ireland

Revised 03/12 PE2444

EXHIBIT 7

Guidance for Industry

Integration of Dose-Counting Mechanisms into MDI Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Clinical Medical
March 2003

Guidance for Industry

Integration of Dose-Counting Mechanisms into MDI Drug Products

Additional copies are available from:

Office of Training and Communications
Division of Communication Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville MD 20857
(Tel): 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Clinical Medical

March 2003

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry [1]
Integration of Dose-Counting Mechanisms into MDI Drug Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers who are developing or plan to develop drug products for oral inhalation using metered-dose inhalers (MDIs). The guidance reflects the Agency's current recommendations regarding the integration of dose-counting mechanisms into MDI drug products for oral inhalation. Although the contents of the guidance should be *considered* by any manufacturer of *any* MDI drug product (including nasal MDI products), this guidance is not specifically intended for manufacturers of already marketed MDI drug products for oral inhalation nor for manufacturers developing MDIs for other routes of administration (e.g., nasal MDIs). It is also not intended for manufacturers developing multidose dry powder inhalers (MDPIs), which already incorporate dose counters as an integral part of the delivery system. Manufacturers developing new MDPIs are encouraged to continue including dose counters in their products and may find the contents of this guidance useful in their planning.

For the purposes of this guidance, the term *dose counter* includes both mechanisms that use a numeric count to indicated doses remaining, as well as dose-indicating mechanisms that do not enumerate the number of actuations, but rather indicate via color coding or other means when a device is nearing the end of its useful life. Also, the use of the term *integrated* in this document is intended to define dose counters that are an integral part of the MDI canister and/or actuator, and not simply an add-on that can be removed and used multiple times with various products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Metered-dose inhalers have been available for nearly 50 years and have come to be regarded as the preferred method of delivery for many important drugs intended to treat obstructive airway diseases, such as asthma, emphysema, and chronic bronchitis.[2] MDIs represent a reliable, convenient dosing device for delivery of medications to the lungs. However, they have one major disadvantage over other dosage forms. Currently available MDIs offer no practical way for patients to track the remaining numbers of doses or amount of medication. A complicating, but necessary design feature of MDIs is that they contain more formulation than strictly required to expel the labeled number of actuations. This additional amount of formulation (propellant, drug substance, and any excipients) is necessary to ensure the dosing consistency of each spray through the labeled number. For instance, an MDI labeled to deliver 120 metered-actuations may expel 20 to 30 additional actuations (depending on the specific fill target for that product). However, the amount of drug per spray in those additional 20 to 30 actuations may in many cases be inconsistent and with continued use beyond the label claim will become negligible. Since the inactive components in the drug formulation may exceed 95 to 99 percent, an MDI used beyond the recommended dose may appear to be delivering a therapeutic spray when it isn't. Other than carefully and consistently tracking each actuation in writing and subtracting this total from the labeled number of actuations, there is no method by which a patient can determine how many effective doses are left in an MDI. Various means of *testing* the inhalers (e.g., shaking the canister) are unreliable and some in addition may damage the MDI (e.g., the *float-test,* placing the canister in water).

Currently, patients must guess how many doses are left in their MDIs and have two practical options: (1) throw away an MDI that may still contain acceptable metered-doses or (2) use a product when it may be beyond the recommended number of doses and risk not receiving the correct drug dose. The former is wasteful, and the latter is potentially dangerous. The addition of an accurate dose counter to an individual MDI unit would allow the patient to reliably track the numbers of actuations used from that individual inhaler (i.e., to identify when the label claim number of actuations has been reached). This would prevent the patient from discarding an inhaler unnecessarily or using the product beyond the recommendations provided in the labeling for that product.

The recommendations in this guidance address primarily MDI products designed to deliver drugs to the lungs for any indication. This is because the consequences of not receiving an acceptable metered dose are more clinically important for oral inhalation drug products than for the current medications available in nasal MDIs. Medications delivered to the lungs often play a vital role in the treatment of airway diseases and are potentially life-saving. Nasally delivered drugs are more typically intended to treat bothersome, but non-life-threatening, conditions. However, if a

[2] *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2,* National Asthma Education and Prevention Program of the National Institutes of Health, NIH publication #97-4051, April 1997.

nasal MDI were developed where the issue of dosing beyond the recommended label claimed number of doses were associated with a more serious consequence, this guidance would be applicable.

Finally, this guidance is not intended to preclude other accurate means of informing patients as to the remaining number of metered-doses left in an MDI. If manufacturers develop other ways apart from the use of a dose counter, the FDA is willing to consider those innovations and, if satisfactory, to deem them reasonable alternatives.

III. INTEGRATION OF DOSE-COUNTING MECHANISMS INTO MDI PRODUCTS UNDER DEVELOPMENT

A. General Recommendations

The Agency recommends that manufacturers with metered-dose inhalers under development for oral inhalation integrate a dose-counting device into the development of their MDI drug product. Dose counters should provide, either through a direct numeric count or color coding, a clear indication of when an MDI is approaching the end of its recommended number of actuations as well as when it has reached or exceeded that number. An indication that an MDI is approaching the end of its recommended number of actuations should occur when a sufficient number of actuations are left to give patients enough time to obtain a new MDI. If a numeric count is chosen, we recommend that the counter be designed so that it counts downward from the recommended number of actuations to zero, rather than counting upwards, enabling patients to know when a device is approaching the end of its life (i.e., the number of actuations is approaching zero).

As previously mentioned, this guidance specifically refers to orally inhaled MDI drug products currently under development or which are being planned for development. Although the integration of dose counters into currently approved MDIs is also encouraged, it is recognized that the economics of doing so may be burdensome, particularly for MDIs using chlorofluorocarbons as propellants (since these products will eventually be universally phased-out under the provisions of the Montreal Protocol on Protection of the Ozone Layer). Manufacturers with MDI drug products in the latter stages of development are encouraged to integrate a dose counter into their product as soon as feasible, although the integration may not be possible prior to submission of a new drug application. In such cases, manufacturers are encouraged to commit to developing an integrated dose counter in the postmarketing period.

B. Reliability Issues

Dose counters should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible. However, if some low frequency of error is unavoidable, the device should be designed to specifically avoid undercounting (i.e., the MDI sprays, but the counter does not advance). Undercounting could result in patients assuming they have medication left in their MDI when they do not, a circumstance that is potentially dangerous. The reliability of dose counters should be established during development under in-vitro testing

(simulating use and potential abuse), as well as in clinical use. The documentation of dose counter functionality, reliability, and accuracy would ideally be derived from assessments in clinical trials including, where possible, phase-3 trials. However, for dose counters added either late in a development program or postapproval, in-use studies should be designed and conducted to obtain this information. Note that in either case, these studies do not need to establish the clinical benefit of incorporating a dose counter, rather, they should address issues related to ergonomics, ruggedness, and accuracy of the counters in clinical settings. The range of patients in whom this information is developed should include reasonable representation of special populations likely to use the drug (e.g., pediatrics, geriatrics). Finally, if the same dose counter design and mechanism is incorporated into multiple different MDIs, it would not ordinarily be necessary to repeat the in-use studies for each additional MDI product in which a counter of the same design is used, once the in-use data have been satisfactorily developed with the device. However, since dosing characteristics vary between MDIs, in-vitro testing would ordinarily be expected in all such cases.

C. Other Considerations

A lock-out mechanism to prevent doses beyond the labeled number of actuations would be an optional feature of dose counters. However, a lock-out feature would not be recommended for bronchodilator medications used to treat acute bronchospasm. For these *rescue bronchodilator*s, the ability of the MDI to actuate beyond the labeled number of actuations and to provide even a partially therapeutic dose of drug could be life saving.

EXHIBIT 8

8475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 08, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *14/103,324*
FILING DATE: *December 11, 2013*
PATENT NUMBER: *9463289*
ISSUE DATE: *October 11, 2016*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No:	14/103,324
Applicant:	Declan Walsh et al.
Filed:	December 11, 2013
Title:	DOSE COUNTERS FOR INHALERS, INHALERS AND METHODS OF ASSEMBLY THEREOF
T.C./A.U.:	2876
Examiner:	Daniel A. Hess
Confirmation No.:	3830
Docket No.:	TEVE-139US1

AMENDMENT UNDER 37 C.F.R. § 1.116

Expedited Procedure

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Responsive to the Final Office Action dated December 7, 2015, please amend the above-identified application as follows:

☐ **Amendments to the Specification** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet(s).

☐ **Amendments to the Abstract** are on page of this paper. A clean version of the Abstract is on page of this paper.

☒ **Remarks/Arguments** begin on page 4 of this paper.

Amendments to the Claims: This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) An inhaler for metered dose inhalation, the inhaler comprising:

a main body having a canister housing,

a medicament canister, which is moveable relative to the canister housing and retained in a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister~~and movable relative thereto~~, and

a dose counter~~, the dose counter~~ having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,

wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall ~~and located directly adjacent the actuation member~~, and

wherein the canister housing has a longitudinal axis X which passes through the center of the central outlet port,

the inner wall canister support formation, the actuation member, and the central outlet port lying in a common plane coincident with the longitudinal axis X.

2. (Previously Presented) The inhaler as claimed in claim 1 wherein the medicament canister is movable relative to the dose counter.

3. (Original) The inhaler as claimed in claim 1 further comprising an aperture formed in the inner wall through which the portion of the actuation member extends.

4. (Original) The inhaler as claimed in claim 1, wherein the first inner wall canister support formation comprises a support rail which extends longitudinally along an inside surface of the main body.

5. (Original) The inhaler as claimed in claim 4, wherein the support rail includes a step formed thereon.

6. (Original) The inhaler as claimed in claim 4 further comprising a plurality of support rails each of which extends longitudinally along an inside surface of the main body.

7. (Original) The inhaler as claimed in claim 6, wherein two of the plurality of support rails are positioned at opposite ends of the inside surface of the main body to face each other.

8. (Original) The inhaler as claimed in claim 4, wherein the support rail includes two steps formed thereon, the steps being spaced apart longitudinally along an inside surface of the main body.

9. (Original) The inhaler as claimed in claim 4, wherein the support rail merges with the inner wall at a location adjacent the aperture.

10. (Original) The inhaler as claimed in claim 9, wherein a width dimension of the support rail is not constant, and the width dimension is greatest at the location where the support rail merges with the inner wall.

11. - 20. (Cancelled)

Remarks/Arguments:

Claim Status

Claims 1-10 are currently pending and stand rejected. Claim 1 has been amended and support for the amendments may be found, *for example*, in the original application at page 11, lines 21 to 27, and in FIGs. 7D and 9. No new matter has been added.

Claim Rejections – 35 USC § 103

Claims 1-10 are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Morton et al. (US 2005/0087191) in view of Davies et al. (US 2006/0107949). The Applicant respectfully requests reconsideration of this rejection for the reasons set forth hereinafter.

In establishing a prima facie case of obviousness, "all of the claim limitations must be considered." M.P.E.P. §2143. Sole independent claim 1 recites features that are neither disclosed nor suggested by the cited references, namely:

> An inhaler for metered dose inhalation, the inhaler comprising: a main body having a canister housing, a medicament canister, which is moveable relative to the canister housing and ***retained in a central outlet port of the canister housing arranged to mate with a canister fire stem of the medicament canister***, and a dose counter having an actuation member having at least a portion thereof located in the canister housing for operation by movement of the medicament canister,
>
> wherein the canister housing has an inner wall, and a first inner wall canister support formation extending inwardly from a main surface of the inner wall***, and***
>
> ***wherein the canister housing has a longitudinal axis X which passes through the center of the central outlet port,***
>
> ***the inner wall canister support formation, the actuation member, and the central outlet port lying in a common plane coincident with the longitudinal axis X***. [Emphasis Added]

By way of background to the instant invention recited in amended claim 1, the dash-dot line shown below depicts how the inner wall canister support formation 144, the actuation member at 74, and the central outlet port 148 lie in a common plane coincident with the longitudinal axis X at 148.

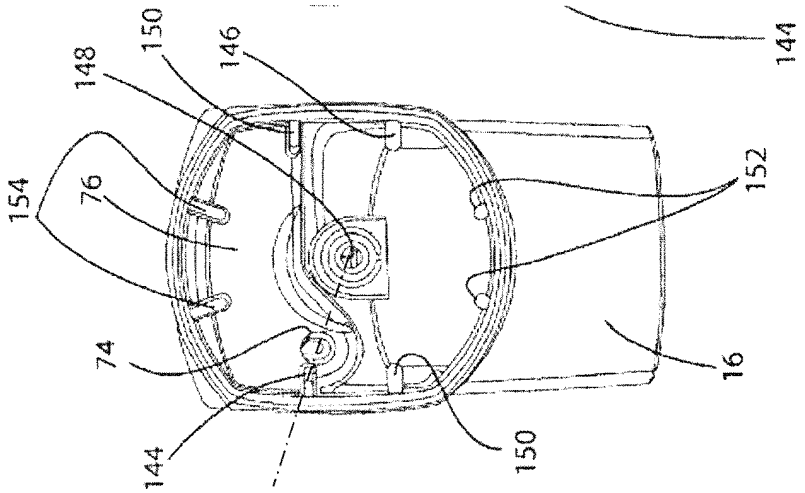
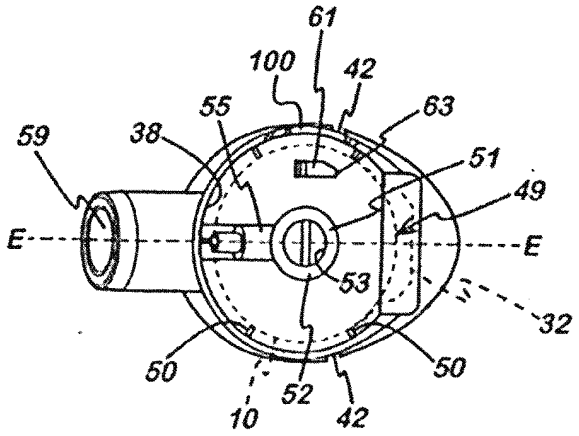


FIG. 7D

As explained in the instant application, this arrangement is "*highly advantageous in that the first inner wall canister support formation can prevent a canister from rocking too much relative to the main body of the inhaler. Since the canister may operate the actuation member of the dose counter, this substantially improves dose counting and avoids counter errors*." Page 11, lines 16-20. Also, as set forth in the instant application, the claimed arrangement has the advantage of preventing the canister from rocking towards the position of the dose counter actuation member, which rocking can change the height of the actuation member and thereby undesirably alter the accuracy of the dose counter (see page 11, lines 25-27, and page 27 lines 23-28). It is worth noting that the magnitude of the rocking does not have to be great for it to have a potentially detrimental effect on counter performance. By way of illustration, on page 31, lines 14-15 of the present application, it is disclosed that the distance between the average start and average reset position of such counters may be about 0.7 mm.

Applicant has discovered that by minimising and/or eliminating the described rocking of the canister in the direction of the actuation member, by way of the specific positioning of a canister support formation relative to the actuator and outlet port, the present invention improves the accuracy of such dose counters. Neither the problem of canister rocking, nor the solution of the specific placement of the canister support formation are taught or suggested by the prior art, which is discussed below.

Turning now to Davies', it is clear that it is not possible to draw a straight line through the center of the stem block (53), the rib (50) and the actuator aperture (61) of FIG. 13 in Davies (below). Accordingly, Davies' inner wall canister support formation, actuation member, and outlet port do not lie in a common plane coincident with the longitudinal axis (near 53). Accordingly, Davies' neither discloses all of the features recited in amended claim 1, nor does Davies' device confer the same benefits as the device that is recited in amended claim 1.



Morton does not disclose the above-identified features of amended claim 1, and the Office Action does not present any arguments to the contrary. Thus, amended claim 1 is not obvious in view of the cited art.

Lastly, the Applicant notes that the Office Action has made the general observation that "*having a gap in the canister housing that is filled by support rails is not functionally better or worse than having a canister housing with less of a gap, more closely conforming to the shape of the housing and obviating the need for the types of rails in the instant invention.*" The Applicant disagrees with this statement. Simply conforming the housing to the shape of the canister would increase the airflow resistance of the inhaler and could affect the ability of users with reduced lung function (e.g., the elderly, young or those suffering from an asthma or COPD

exacerbation) to draw air through the inhaler and inhale medicament effectively. Accordingly, using a body with a greater clearance and accompanying support ribs provides increased design flexibility and a tangible benefit over the approach set forth in the Office Action.

Accordingly, because claim 1 includes features that are neither disclosed nor suggested by the cited references, *prima facie* obviousness cannot be established based on the cited references. The dependent claims that stand rejected should also be allowed at least as being dependent upon an allowable base claim. Reconsideration of claims 1-10 is respectfully requested.

Conclusion

In view of the remarks set forth above, the Applicant respectfully submits that this application is now in condition for allowance, which action is respectfully requested. If the Examiner believes an interview will advance the prosecution of this application, it is respectfully requested that the Examiner contact the undersigned to arrange the same.

Respectfully submitted,

/Brett J. Rosen/

Brett J. Rosen, Reg. No. 56,047
Attorney for Applicants

BJR/mf

Dated: March 7, 2016

P.O. Box 980
Valley Forge, PA 19482
(610) 407-0700

The Director is hereby authorized to charge or credit Deposit Account No. **18-0350** for any additional fees, or any underpayment or credit for overpayment in connection herewith.

2935779

EXHIBIT 9

Merriam-Webster's Medical Desk Dictionary

DELMAR CENGAGE Learning

Australia • Brazil • Japan • Korea • Mexico • Singapore • Spain • United Kingdom • United States

DELMAR
CENGAGE Learning

Merriam-Websters Medical Desk Dictionary

Library of Congress Control Number: 2001058656

ISBN-13: 978-1-4180-0056-1

ISBN-10: 1-4180-0056-6

Delmar
Executive Woods
5 Maxwell Drive
Clifton Park, NY 12065
USA

Cengage Learning is a leading provider of customized learning solutions with office locations around the globe, including Singapore, the United Kingdom, Australia, Mexico, Brazil, and Japan. Locate your local office at **www.cengage.com/global**

Cengage Learning products are represented in Canada by Nelson Education, Ltd.

To learn more about Delmar, visit **www.cengage.com/delmar**

Purchase any of our products at your local bookstore or at our preferred online store **www.cengagebrain.com**

Printed in the United States of America
14 15 14 13

in•fra•tem•po•ral \ˌin-frə-ˈtem-p(ə-)rəl\ *adj* : situated below the temporal fossa

infratemporal crest *n* : a transverse ridge on the outer surface of the greater wing of the sphenoid bone that divides it into a superior portion that contributes to the formation of the temporal fossa and an inferior portion that contributes to the formation of the infratemporal fossa

infratemporal fossa *n* : a fossa that is bounded above by the plane of the zygomatic arch, laterally by the ramus of the mandible, and medially by the pterygoid plate, and that contains the masseter and pterygoid muscles and the mandibular nerve

in•fra•ten•to•ri•al \ˌin-frə-ten-ˈtōr-ē-əl\ *adj* : occurring or made below the tentorium cerebelli ⟨an ~ tumor⟩

in•fra•um•bil•i•cal \-ˌəm-ˈbil-i-kəl *also* -ˌəm-bə-ˈlī-kəl\ *adj* : situated below the navel

in•fra•ver•sion \ˌin-frə-ˈvər-zhən\ *n* : INFRAOCCLUSION

infundibula *pl of* INFUNDIBULUM

in•fun•dib•u•lar \ˌin-(ˌ)fən-ˈdib-yə-lər\ *adj* **1** : INFUNDIBULIFORM **2** : of, relating to, affecting, situated near, or having an infundibulum ⟨~ stenosis⟩

infundibular process *n* : NEURAL LOBE

infundibular recess *n* : a funnel-shaped downward prolongation of the floor of the third ventricle of the brain behind the optic chiasma into the infundibulum of the pineal gland

in•fun•dib•u•li•form \-lə-ˌfȯrm\ *adj* : having the form of a funnel or cone

in•fun•dib•u•lo•pel•vic ligament \ˌin-fən-ˌdib-yə-lō-ˈpel-vik-\ *n* : SUSPENSORY LIGAMENT OF THE OVARY

in•fun•dib•u•lum \ˌin-(ˌ)fən-ˈdib-yə-ləm\ *n, pl* **-la** \-lə\ : any of various conical or dilated organs or parts: **a** : the hollow conical process of gray matter that is borne on the tuber cinereum and constitutes the stalk of the neurohypophysis by which the pituitary gland is continuous with the brain — called also *neural stalk* **b** : any of the small spaces having walls beset with air sacs in which the bronchial tubes terminate in the lungs **c** : CONUS ARTERIOSUS **d** : the passage by which the anterior ethmoidal air cells and the frontal sinuses communicate with the nose **e** : the abdominal opening of a fallopian tube

in•fuse \in-ˈfyüz\ *vb* **in•fused; in•fus•ing** *vt* **1** : to steep in liquid (as water) without boiling so as to extract the soluble constituents or principles **2** : to administer or inject by infusion esp. intravenously ⟨~ the blood with glucose⟩ ⟨~ a solution of lactate⟩ ~ *vi* : to administer a solution by infusion

in•fusion \in-ˈfyü-zhən\ *n* **1 a** : the introducing of a solution (as of glucose or salt) esp. into a vein; *also* : the solution so used **b** (1) : the steeping or soaking usu. in water of a substance (as a plant drug) in order to extract its soluble constituents or principles — compare DECOCTION 1 (2) : the liquid extract obtained by this process **2** : a watery suspension of decaying organic material ⟨culturing soil amebas in lettuce ~⟩

infusion pump *n* : a device that releases a measured amount of a substance in a specific period of time

in•fu•so•ria \ˌin-fyü-ˈzȯr-ē-ə, -ˈsȯr-\ *n pl, often cap* : organisms that are infusorians — not used technically

in•fu•so•ri•an \-ē-ən\ *n* : any of a heterogeneous group of minute organisms found esp. in water with decomposing organic matter; *esp* : a ciliated protozoan — **infusorian** *adj*

in•gest \in-ˈjest\ *vt* : to take in for or as if for digestion

in•ges•ta \in-ˈjes-tə\ *n pl* : material taken into the body by way of the digestive tract

in•ges•tant \-tənt\ *n* : something taken into the body by ingestion; *esp* : an allergen so taken

in•gest•ible \in-ˈjes-tə-bəl\ *adj* : capable of being ingested ⟨~ capsules⟩

in•ges•tion \in-ˈjes(h)-chən\ *n* : the taking of material (as food) into the digestive system

in•gest•ive \in-ˈjes-tiv\ *adj* : of or relating to ingestion ⟨~ behavior⟩

in•glu•vi•es \in-ˈglü-vē-ˌēz\ *n, pl* **ingluvies** : CROP

in•glu•vi•itis \in-ˌglü-vē-ˈī-təs\ *or* **in•glu•vi•tis** \ˌin-glü-ˈvīt-əs\ *n* : catarrhal inflammation of the crop in fowls

in•gra•ves•cence \ˌin-grə-ˈves-ᵊn(t)s\ *n* : the state of becoming progressively more severe ⟨persistence and ~ of behavior disorders, in spite of improved circumstances —Norman Cameron⟩

in•gre•di•ent \in-ˈgrēd-ē-ənt\ *n* : something that enters into a compound or is a component part of any combination or mixture ⟨formula which will have just about the same ~*s* as mother's milk —Morris Fishbein⟩ — **ingredient** *adj*

in•grow•ing \ˈin-ˌgrō-iŋ\ *adj* : growing or tending inward : INGROWN ⟨~ hairs⟩

in•grown \ˈin-ˌgrōn\ *adj* : grown in; *specif* : having the normally free tip or edge embedded in the flesh ⟨an ~ toenail⟩

in•growth \ˈin-ˌgrōth\ *n* **1** : a growing inward (as to fill a void) ⟨~ of cells⟩ **2** : something that grows in or into a space ⟨lymphoid ~*s*⟩

in•guen \ˈiŋ-gwən, -ˌgwen\ *n, pl* **in•gui•na** \-gwə-nə\ : GROIN

in•gui•nal \ˈiŋ-gwən-ᵊl\ *adj* **1** : of, relating to, or situated in the region of the groin **2** : ILIAC 2 ⟨the ~ abdominal region⟩ — **in•gui•nal•ly** *adv*

inguinal canal *n* : a passage about one and one half inches (4 centimeters) long that lies parallel to and a half inch above the inguinal ligament: as **a** : a passage in the male through which the testis descends into the scrotum and in which the spermatic cord lies — called also *spermatic canal* **b** : a passage in the female accommodating the round ligament

inguinale — see GRANULOMA INGUINALE, LYMPHOGRANULOMA INGUINALE

inguinal gland *n* : INGUINAL NODE

inguinal hernia *n* : a hernia in which part of the intestine protrudes into the inguinal canal

inguinal ligament *n* : the thickened lower border of the aponeurosis of the external oblique muscle of the abdomen that extends from the anterior superior iliac spine to the pubic tubercle, is continuous with the fascia lata near the thigh, and forms the external pillar of the superficial inguinal ring and a part of the anterior boundary of the femoral ring — called also *Poupart's ligament*

inguinal node *n* : any of the superficial lymphatic nodes of the groin made up of two more or less distinct groups of which one is disposed along the inguinal ligament and the other about the saphenous opening — called also *inguinal gland*

inguinal ring *n* : either of two openings in the fasciae of the abdominal muscles on each side of the body that are the inlet and outlet of the inguinal canal, give passage to the spermatic cord in the male and the round ligament in the female, and are a frequent site of hernia formation : ABDOMINAL RING: **a** : DEEP INGUINAL RING **b** : SUPERFICIAL INGUINAL RING

INH *abbr* isoniazid

¹in•ha•lant *also* **in•ha•lent** \in-ˈhā-lənt\ *n* **1** : something (as an allergen or an anesthetic vapor) that is inhaled **2** : any of various often toxic volatile substances (as spray paint, glue, or paint thinner) whose fumes are sometimes inhaled for their euphoric effect

²inhalant *also* **inhalent** *adj* : used for inhaling or constituting an inhalant ⟨~ anesthetics⟩

in•ha•la•tion \ˌin-(h)ə-ˈlā-shən, ˌin-ᵊl-ˈā-\ *n* **1** : the act or an instance of inhaling; *specif* : the action of drawing air into the lungs by means of a complex of essentially reflex actions that involve changes in the diaphragm and in muscles of the abdomen and thorax which cause enlargement of the chest cavity and lungs resulting in production of relatively negative pressure within the lungs so that air flows in until the pressure is restored to equality with that of the atmosphere **2** : material (as medication) to be taken in by inhaling — **in•ha•la•tion•al** \-shnəl, -shən-ᵊl\ *adj*

inhalation therapist *n* : a specialist in inhalation therapy

inhalation therapy *n* : the therapeutic use of inhaled gases and esp. oxygen (as in the treatment of respiratory disease)

in•ha•la•tor \ˈin-(h)ə-ˌlāt-ər, ˈin-ᵊl-ˌāt-\ *n* : a device providing a mixture of oxygen and carbon dioxide for breathing that is

used esp. in conjunction with artificial respiration — compare INHALER

in·hale \in-ˈhā(ə)l\ *vb* **in·haled; in·hal·ing** *vt* : to draw in by breathing ~ *vi* : to breathe in

inhalent *var of* INHALANT

in·hal·er \in-ˈhā-lər\ *n* : a device by means of which usu. medicinal material is inhaled — compare INHALATOR

in·her·ent \in-ˈhir-ənt, in-ˈher-\ *adj* : involved in the constitution or essential character of something : belonging by nature ⟨the skin's ~ elasticity —Kathleen C. Engles⟩ — **in·her·ent·ly** *adv*

in·her·it \in-ˈher-ət\ *vt* : to receive from a parent or ancestor by genetic transmission

in·her·it·able \in-ˈher-ət-ə-bəl\ *adj* : capable of being transmitted from parent to offspring genetically — **in·her·it·abil·i·ty** \-ˌher-ət-ə-ˈbil-ət-ē\ *n, pl* **-ties**

in·her·i·tance \in-ˈher-ət-ən(t)s\ *n* **1** : the reception of genetic qualities by transmission from parent to offspring **2** : all of the genetic characters or qualities transmitted from parent to offspring — compare GENOTYPE 2, PHENOTYPE

in·hib·in \in-ˈhib-ən\ *n* : a glycoprotein hormone that is secreted by the pituitary gland and in the male by the Sertoli cells and in the female by the granulosa cells and that inhibits the secretion of follicle-stimulating hormone

in·hib·it \in-ˈhib-ət\ *vt* **1 a** : to restrain from free or spontaneous activity esp. through the operation of inner psychological or external social constraints ⟨an ~*ed* person⟩ **b** : to check or restrain the force or vitality of ⟨~ aggressive tendencies⟩ **2 a** : to reduce or suppress the activity of ⟨a presynaptic neuron can not only excite a postsynaptic neuron but can also ~ it —H. W. Kendler⟩ **b** : to retard or prevent the formation of **c** : to retard, interfere with, or prevent (a process or reaction) ⟨~ ovulation⟩

in·hib·it·able \-ə-bəl\ *adj* : capable of being inhibited

in·hi·bi·tion \ˌin-(h)ə-ˈbish-ən\ *n* : the act or an instance of inhibiting or the state of being inhibited: as **a** (1) : a stopping or checking of a bodily action : a restraining of the function of an organ or an agent (as a digestive fluid or enzyme) ⟨~ of the heartbeat by stimulation of the vagus nerve⟩ ⟨~ of plantar reflexes⟩ (2) : interference with or retardation or prevention of a process or activity ⟨~ of bacterial growth⟩ **b** (1) : a desirable restraint or check upon the free or spontaneous instincts or impulses of an individual guided or directed by the social and cultural forces of the environment ⟨the self-control so developed is called ~ —C. W. Russell⟩ (2) : a neurotic restraint upon a normal or beneficial impulse or activity caused by psychological inner conflicts or by sociocultural forces of the environment ⟨other outspoken neurotic manifestations are general ~*s* such as inability to think, to concentrate —Muriel Ivimey⟩ ⟨~*s*, phobias, compulsions, and other neurotic patterns —*Psychological Abstracts*⟩

in·hib·i·tor \in-ˈhib-ət-ər\ *n* : one that inhibits: as **a** : an agent that slows or interferes with a chemical reaction **b** : a substance that reduces the activity of another substance (as an enzyme) **c** : a gene that checks the normal effect of another nonallelic gene when both are present

in·hib·i·to·ry \in-ˈhib-ə-ˌtōr-ē, -ˌtȯr-\ *adj* : of, relating to, or producing inhibition : tending or serving to inhibit

inhibitory postsynaptic potential *n* : increased negativity of the membrane potential of a neuron on the postsynaptic side of a nerve synapse that is caused by a neurotransmitter (as gamma-aminobutyric acid) which renders the membrane selectively permeable to potassium and chloride ions on the inside but not to sodium ions on the outside and that tends to inhibit the neuron since an added increase in potential in the positive direction is needed for excitation — abbr. *IPSP*

in·ho·mo·ge·ne·ity \ˌin-ˌhō-mə-jə-ˈnē-ət-ē, -ˈnā-; *esp Brit* -ˌhäm-ə-\ *n, pl* **-ities** : lack of homogeneity — **in·ho·mo·ge·neous** \ˌin-ˌhō-mə-ˈjē-nē-əs\ *adj*

in·i·ac \ˈin-ē-ˌak\ *adj* : relating to the inion

in·i·en·ceph·a·lus \ˌin-ē-in-ˈsef-ə-ləs\ *n* : a teratological fetus with a fissure in the occiput through which the brain protrudes — **in·i·en·ce·phal·ic** \ˌin-ē-ˌen-sə-ˈfal-ik\ *adj*

in·i·en·ceph·a·ly \-ˈsef-ə-lē\ *n, pl* **-lies** : the condition of being an iniencephalus

in·i·on \ˈin-ē-ˌän, -ən\ *n* : OCCIPITAL PROTUBERANCE a

ini·ti·a·tion codon \in-ˌish-ē-ˈā-shən-\ *n* : a codon that stimulates the binding of a transfer RNA which starts protein synthesis — called also *initiator codon;* compare TERMINATOR

ini·ti·a·tor \in-ˈish-ē-ˌāt-ər\ *n* : one that initiates: as **a** : a substance that initiates a chemical reaction **b** : a substance that produces an irreversible change in bodily tissue causing it to respond to other substances which promote the growth of tumors

inj *abbr* injection

in·ject \in-ˈjekt\ *vt* **1** : to force a fluid into (a vessel, cavity, or tissue) for preserving, hardening, or coloring structures **2** : to introduce (as by injection or gravity flow) a fluid into (a living body) esp. for the purpose of restoring fluid balance, treating nutritional deficiencies or disease, or relieving pain; *also* : to treat (an individual) with injections

[1]in·ject·able \-ˈjek-tə-bəl\ *adj* : capable of being injected ⟨~ medications⟩

[2]injectable *n* : an injectable substance (as a drug)

in·jec·tant \-ˈjek-tənt\ *n* : an allergen that is injected

injected *adj* : CONGESTED ⟨the tonsils were hypertrophied and ~ —*Jour. Amer. Med. Assoc.*⟩

in·jec·tion \in-ˈjek-shən\ *n* **1 a** : the act or an instance of injecting a drug or other substance into the body **b** : a solution (as of a drug) intended for injection (as by catheter or hypodermic syringe) either under or through the skin or into the tissues, a vein, or a body cavity **c** : an act or process of injecting vessels or tissues; *also* : a specimen prepared by injection **2** : the state of being injected : CONGESTION — see CIRCUMCORNEAL INJECTION

in·jec·tor \in-ˈjek-tər\ *n* : a device for injecting or making an injection

in·jure \ˈin-jər\ *vt* **in·jured; in·jur·ing** \ˈinj-(ə-)riŋ\ **1** : to inflict bodily hurt on **2** : to impair the soundness of ⟨~ your health⟩

in·ju·ri·ous \in-ˈjůr-ē-əs\ *adj* : inflicting or tending to inflict injury ⟨~ to health⟩ — **in·ju·ri·ous·ly** *adv*

in·ju·ry \ˈinj-(ə-)rē\ *n, pl* **-ries** : hurt, damage, or loss sustained

injury potential *n* : the difference in electrical potential between the injured and uninjured parts of a nerve or muscle — called also *demarcation potential*

ink·blot \ˈiŋk-ˌblät\ *n* : any of several plates showing blots of ink for use in psychological testing

inkblot test *n* : any of several psychological tests (as a Rorschach test) based on the interpretation of irregular figures (as blots of ink)

in·lay \ˈin-ˌlā\ *n* **1** : a tooth filling shaped to fit a cavity and then cemented into place **2** : a piece of tissue (as bone) laid into the site of missing tissue to cover a defect

in·let \ˈin-ˌlet, -lət\ *n* : the upper opening of a bodily cavity; *esp* : that of the cavity of the true pelvis bounded by the pelvic brim

in·mate \ˈin-ˌmāt\ *n* : one of a group occupying a single place of residence; *esp* : a person confined (as in a psychiatric hospital) esp. for a long time

in·nards \ˈin-ərdz\ *n pl* : the internal organs of a human being or animal; *esp* : VISCERA

in·nate \in-ˈāt, ˈin-ˌ\ *adj* : existing in, belonging to, or determined by factors present in an individual from birth : NATIVE, INBORN ⟨~ behavior⟩ — **in·nate·ly** *adv* — **in·nate·ness** *n*

in·ner cell mass \ˌin-ər-\ *n* : the portion of the blastocyst of a mammalian embryo that is destined to become the embryo proper

in·ner–di·rect·ed \ˌin-ər-də-ˈrek-təd, -(ˌ)dī-\ *adj* : directed in

EXHIBIT 10

8475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 08, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *15/269,249*
FILING DATE: *September 19, 2016*
PATENT NUMBER: *9808587*
ISSUE DATE: *November 07, 2017*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 486 227 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
15.12.2004 Bulletin 2004/51

(51) Int Cl.[7]: **A61M 15/00**

(21) Application number: **04020854.8**

(22) Date of filing: **23.06.2001**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **23.06.2000 US 213668 P**
23.06.2000 US 213382 P

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
01948661.2 / 1 330 280

(71) Applicant: **NORTON HEALTHCARE LIMITED**
London E16 2QJ (GB)

(72) Inventors:
- **Keane, Lawrence**
  Bishop Stortford Hertfordshire CM2 3EP (GB)
- **O'Leary, David**
  Essex RM17 6UG (GB)

(74) Representative: **Hill, Justin John et al**
McDermott, Will & Emery,
7 Bishopsgate
London EC2N 3AR (GB)

Remarks:
This application was filed on 02 - 09 - 2004 as a divisional application to the application mentioned under INID code 62.

(54) Medicament inhaler

(57) A new and improved inhaler includes an accurate and consistent mechanical dose metering system that dispenses dry powdered medicament in discrete amounts or doses for patient inhalation, a pressure relief system that manages pressure within a medicament reservoir of the inhaler to ensure consistently dispensed doses, and a dose counting system indicating the number of doses remaining in the inhaler.

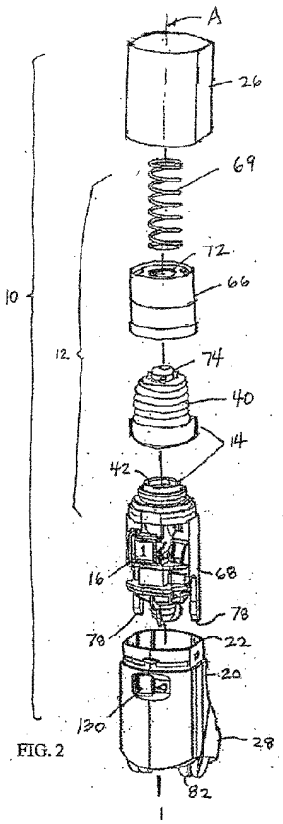


FIG. 2

EP 1 486 227 A2

Printed by Jouve, 75001 PARIS (FR)

Description

Cross-Reference to Related Applications

[0001] The present application claims priority to co-pending provisional U.S. patent application serial no. 60/213,668, filed June 23, 2000 (entitled "Breath-Actuated Dry Powder Inhaler"), and co-pending provisional U.S. patent application serial no. 60/213,382, filed June 23, 2000 (entitled "De-Agglomerator for Breath-Actuated Dry Powder Inhaler"). Each of these co-pending applications is assigned to the assignee of the present disclosure and incorporated herein by reference.

Field of the Disclosure

[0002] The present disclosure relates to an apparatus and method for administering medicament for inhalation by a patient and, more particularly, to a dry powdered medicament inhaler.

Background of the Disclosure

[0003] Metered dose medicament inhalers are well known for dispensing medicament to the lungs of a patient, for treating asthma for example. Existing types of medicament dispensing inhalers include pressurized propellant inhalers, aqueous solution inhalers, and dry-powdered inhalers.

[0004] U.S. Patent No. 5,503,144 to Bacon, for example, shows a dry powdered inhaler. The inhaler includes a reservoir for containing a dry powdered medicament, a metering chamber for removal of the powdered medicament from the reservoir in discrete amounts, and an air inlet for entraining the removed powdered medicament through a mouthpiece upon patient inhalation.

[0005] Another example is U.S. Patent No. 5,971,951 to Ruskewicz, which shows an inhaler including a motor driven cam mechanism for extruding aqueous medicament through a porous membrane to form a medicament aerosol for inhalation by a patient. The inhaler also includes sensors, circuitry and a microprocessor that determines the rate of patient inhalation and operates the extrusion mechanism only upon adequate inhalation levels.

[0006] A pressurized propellant, or "aerosol" inhaler is shown in U.S. Patent No. 5,447,150 to Bacon, which also discloses a simple, mechanical actuation assembly for ensuring that medicament is dispensed from the inhaler only upon adequate inhalation by a patient. The actuation assembly works by applying a pre-load to a valve of the aerosol container sufficient to cause a dose release, but prevents the release by applying a pneumatic resisting force. The dose of medicament is then released upon a patient inhalation strong enough to move a door within the assembly, which in turn releases the pneumatic resisting force.

[0007] What is still desired, however, is a new and improved inhaler for administering medicament for patient inhalation. Preferably, the new and improved inhaler can be used with dry powdered medicament. In addition, the new and improved inhaler will preferably include mechanical assemblies for metering doses of medicament, managing medicament reservoir pressure, and counting the number of doses remaining in the inhaler.

Summary of the Disclosure

[0008] The present disclosure, therefore, provides a new and improved medicament inhaler having a unique dose metering system. The inhaler includes a mouthpiece for patient inhalation, a delivery passageway for directing an inhalation induced air flow through the mouthpiece, a channel extending from the delivery passageway, and a reservoir for containing medicament, with the reservoir having a dispenser port connected to the channel. In a preferred form, the dose metering system includes a cup received in the channel, which is movable between the dispenser port and the delivery passageway, a cup spring biasing the cup towards one of the dispenser port and the passageway, and a yoke movable between at least two positions. The yoke includes a ratchet engaging the cup and preventing movement of the cup when the yoke is in one of the positions, and allowing movement of the cup when the yoke is in another of the positions.

[0009] The present disclosure also provides a medicament inhaler having a unique reservoir pressure system. The inhaler includes a sealed reservoir having a dispenser port, and a channel communicating with the dispenser port, and a cup assembly movably received in the channel. In a preferred form, the pressure system includes a pressure relief port in the channel, and a conduit providing fluid communication between an interior of the sealed reservoir and the pressure relief port of the channel. The cup assembly includes a recess adapted to receive medicament when aligned with the dispenser port, a first sealing surface adapted to seal the dispenser port when the recess is unaligned with the dispenser port, and a second sealing surface adapted to seal the pressure relief port when the recess is aligned with the dispenser port and unseal the pressure relief port when the recess is unaligned with the dispenser port.

[0010] The present disclosure additionally provides a medicament inhaler having a unique dose counter. The inhaler includes a mouthpiece for patient inhalation, a dose metering system including a pawl movable along a predetermined path during the metering of a dose of medicament to the mouthpiece by the dose metering system, and a dose counter. In a preferred form, the dose counter includes a bobbin, a rotatable spool, and a rolled ribbon received on the bobbin, rotatable about an axis of the bobbin. The ribbon has indicia thereon successively extending between a first end of the ribbon secured to the spool and a second end of the ribbon positioned on the bobbin. The dose counter also in-

cludes teeth extending radially outwardly from the spool into the predetermined path of the pawl so that the spool is rotated by the pawl and the ribbon advanced onto the spool during the metering of a dose to the mouthpiece.

[0011] Thus, the present disclosure provides a new and improved inhaler including a simple, accurate and consistent mechanical dose metering system that dispenses dry powdered medicament in discrete amounts or doses for patient inhalation, a reservoir pressure system that ensures consistently dispensed doses, and a dose counter indicating the number of doses remaining in the inhaler.

[0012] Further features and advantages of the presently disclosed inhaler will become more readily apparent to those having ordinary skill in the art to which the present disclosure relates from the drawings and the detailed description.

Brief Description of the Drawings

[0013] So that those having ordinary skill in the art will more readily understand how to construct a dry powdered medicament inhaler in accordance with the present disclosure, a preferred embodiment is described below with reference to the drawing figures wherein:

FIG. 1 is a first side isometric view of a dry powdered medicament inhaler according to the present disclosure;

FIG. 2 is an exploded, second side isometric view of the inhaler of FIG. 1;

FIG. 3 is a second side isometric view of a main assembly of the inhaler of FIG. 1;

FIG. 4 is a second side isometric view of the main assembly of the inhaler of FIG. 1, shown with a yoke removed;

FIG. 5 is an exploded first side isometric view of the main assembly of the inhaler of FIG. 1;

FIG. 6 is an exploded enlarged isometric view of a medicament cup of the inhaler of FIG. 1;

FIG. 7 is an exploded first side isometric view of a hopper and a de-agglomerator of the inhaler of FIG. 1;

FIG. 8 is an exploded second side isometric view of the hopper and a swirl chamber roof of the de-agglomerator of the inhaler of FIG. 1;

FIG. 9 is an exploded first side isometric view of a case, cams and a mouthpiece cover of the inhaler of FIG. 1;

FIG. 10 is an enlarged side isometric view of one of the cams of the inhaler of FIG. 1;

FIG. 11 is a second side isometric view of the yoke of the inhaler of FIG. 1;

FIG. 12 is a first side isometric view of the yoke of the inhaler of FIG. 1, showing a ratchet and a push bar of the yoke;

FIG. 13 is a schematic illustration of lateral movement of a boss of the medicament cup in response to longitudinal movement of the ratchet and the push bar of the yoke of the inhaler of FIG. 1;

FIG. 14 is an enlarged isometric view of a dose counter of the inhaler of FIG. 1;

FIG. 15 is an exploded enlarged isometric view of the dose counter of the inhaler of FIG. 1; and

FIG. 16 is an enlarged isometric view, partially in section, of a portion of the inhaler of FIG. 1 illustrating medicament inhalation through the inhaler.

[0014] Like reference characters designate identical or corresponding components and units throughout the several views.

Detailed Description of the Preferred Embodiments

[0015] Referring to FIGS. 1 through 16, the present disclosure provides a new and improved inhaler 10 for dispensing a dry-powdered medicament in metered doses for patient inhalation. The inhaler 10 of the present disclosure provides many beneficial features including but not limited to a dose metering system that dispenses dry powdered medicament in discrete amounts or doses for patient inhalation, a medicament reservoir pressure system for managing pressure within the reservoir, and a dose counting system indicating the number of doses remaining in the inhaler 10.

[0016] The inhaler 10 generally includes a housing 18, and an assembly 12 received in the housing (see FIG. 2). The housing 18 includes a case 20 having an open end 22 and a mouthpiece 24 for patient inhalation, a cap 26 secured to and closing the open end 22 of the case 20, and a cover 28 pivotally mounted to the case 20 for covering the mouthpiece 24 (see FIGS. 1, 2 and 9). The housing 18 is preferably manufactured from a plastic such as polypropylene, acetal or moulded polystyrene, but may be manufactured from metal or another suitable material.

[0017] The internal assembly 12 includes a reservoir 14 for containing dry powered medicament in bulk form, a de-agglomerator 32 that breaks down the medicament between a delivery passageway 34 and the mouthpiece 24, and a spacer 38 connecting the reservoir to the de-

agglomerator.

Reservoir

[0018] The reservoir 14 is generally made up of a collapsible bellows 40 and a hopper 42 having an dispenser port 44 (see FIGS. 2-5 and 7-8) for dispensing medicament upon the bellows 40 being at least partially collapsed to reduce the internal volume of the reservoir. The hopper 42 is for holding the dry powder medicament in bulk form and has an open end 46 closed by the flexible accordion-like bellows 40 in a substantially air-tight manner. An air filter 48 covers the open end 46 of the hopper 42 and prevents dry powder medicament from leaking from the hopper 42 (see FIG. 7).

Spacer

[0019] A base 50 of the hopper 42 is secured to a spacer 38, which is in turn secured to the de-agglomerator 32 (see FIGS. 3-5 and 7-8). The hopper 42, the spacer 38, and the de-agglomerator 32 are preferably manufactured from a plastic such as polypropylene, acetal or moulded polystyrene, but may be manufactured from metal or another suitable material. The hopper 42, the spacer 38 and the de-agglomerator 32 are connected in a manner that provides an air tight seal between the parts. For this purpose heat or cold sealing, laser welding or ultrasonic welding could be used, for example.

[0020] The spacer 38 and the hopper 42 together define the medicament delivery passageway 34, which preferably includes a venturi 36 (see FIG. 16) for creating an entraining air flow. The spacer 3 8 defines a slide channel 52 communicating with the dispenser port 44 of the hopper 42, and a chimney 54 providing fluid communication between the medicament delivery passageway 34 and a supply port 56 of the de-agglomerator 32 (see FIGS. 7 and 8). The slide channel 52 extends generally normal with respect to the axis "A" of the inhaler 10.

De-Agglomerator

[0021] As its name implies, the de-agglomerator 32 breaks down agglomerates of dry powder medicament before the dry powder leaves the inhaler 10 through the mouthpiece 24. The de-agglomerator includes a swirl chamber 58 extending from the supply port 56 to an outlet port 60 connected to the mouthpiece 24 (see FIG. 16). The de-agglomerator 32 also includes two diametrically opposed inlet ports 62 that extend substantially tangential to the circular cross-section of the swirl chamber. Radial vanes 64 are positioned at the top of the swirl chamber and are sized such that at least a portion of breath-actuated air streams entering through the diametrically opposed inlet ports 62 collide with the vanes.

[0022] The inhaler 10 preferably includes a de-agglomerator of the type disclosed in co-pending provisional U.S. patent application serial no. 60/213,382, filed June 23, 2000 (entitled "De-Agglomerator for Breath-Actuated Dry Powder Inhaler 10"), which has been incorporated herein by reference. It should be understood that although the inhaler 10 of the present disclosure is shown with a particular de-agglomerator 32, the inhaler 10 is not limited to use with the de-agglomerator shown and can be used with other types of de-agglomerators or a simple swirl chamber.

Dose Metering System

[0023] The dose metering system includes a first yoke 66 and a second yoke 68 mounted on the internal assembly 12 within the housing 18, and movable in a linear direction parallel with an axis "A" of the inhaler 10 (see FIG. 2). An actuation spring 69 is positioned between the cap 26 of the housing 18 and the first yoke 66 for biasing the yokes in a first direction towards the mouthpiece 24. In particular, the actuation spring 69 biases the first yoke 66 against the bellows 40 and the second yoke 68 against cams 70 mounted on the mouthpiece cover 28 (see FIG. 9).

[0024] The first yoke 66 includes an opening 72 that receives and retains a crown 74 of the bellows 40 such that the first yoke 66 pulls and expands the bellows 40 when moved towards the cap 26, i.e., against the actuation spring 69 (see FIG. 2). The second yoke 68 includes a belt 76, which receives the first yoke 66, and two cam followers 78 extending from the belt in a direction opposite the first yoke 66 (see FIGS. 3, 11 and 12), towards the cams 70 of the mouthpiece cover 28.

[0025] The dose metering system also includes the two cams 70 mounted on the mouthpiece cover 28 (see FIGS. 9 and 10), and movable with the cover 28 between open and closed positions. The cams 70 each include an opening 80 for allowing outwardly extending hinges 82 of the case 20 to pass therethrough and be received in first recesses 84 of the cover 28. The cams 70 also include bosses 86 extending outwardly and received in second recesses 88 of the cover 28, such that the cover 28 pivots about the hinges 82 and the cams 70 move with the cover 28 about the hinges.

[0026] Each cam 70 also includes first, second and third cam surfaces 90, 92, 94, and the cam followers 78 of the second yoke 68 are biased against the cam surfaces by the actuation spring 69. The cam surfaces 90, 92, 94 are arranged such the cam followers 78 successively engage the first cam surfaces 90 when the cover 28 is closed, the second cam surfaces 92 when the cover 28 is partially opened, and the third cam surfaces 94 when the cover 28 is fully opened. The first cam surfaces 90 are spaced further from the hinges 82 than the second and the third cam surfaces, while the second cam surfaces 92 are spaced further from the hinges 82 than the third cam surfaces 94. The cams 70, therefore, allow the yokes 66, 68 to be moved by the actuation spring

69 parallel with the axis "A" of the inhaler 10 in the first direction (towards the mouthpiece 24) through first, second and third positions as the cover 28 is opened. The cams 70 also push the yokes 66, 68 in a second direction parallel with the axis "A" (against the actuation spring 69 and towards the cap 26 of the housing 18) through the third, the second and the first positions as the cover 28 is closed.

[0027] The dose metering system further includes a cup assembly 96 movable between the dispenser port 44 of the reservoir 14 and the delivery passageway 34. The cup assembly 96 includes a medicament cup 98 mounted in a sled 100 slidably received in the slide channel 52 of the spacer 38 below the hopper 42 (see FIGS. 5 and 6). The medicament cup 98 includes a recess 102 adapted to receive medicament from the dispenser port 44 of the reservoir 14 and sized to hold a predetermined dose of dry powdered medicament when filled. The cup sled 100 is biased along the slide channel 52 from the dispenser port 44 of the hopper 42 towards the delivery passageway 34 by a cup spring 104, which is secured on the hopper 42 (see FIGS. 4 and 5).

[0028] The dose metering system also includes a ratchet 106 and a push bar 108 on one of the cam followers 78 of the second yoke 68 that engage a boss 110 of the cup sled 100 (see FIGS. 5, 11 and 12). The ratchet 106 is mounted on a flexible flap 112 and is shaped to allow the boss 110 of the sled 100 to depress and pass over the ratchet 106, when the boss 110 is engaged by the push bar 108. Operation of the dose metering system is discussed below.

Reservoir Pressure System

[0029] The reservoir pressure system includes a pressure relief conduit 114 in fluid communication with the interior of the reservoir 14 (see FIGS. 7 and 8), and a pressure relief port 116 in a wall of the slide channel 52 (see FIGS. 5 and 8) providing fluid communication with the pressure relief conduit 114 of the hopper 42.

[0030] The medicament cup assembly 96 includes a first sealing surface 118 adapted to seal the dispenser port 44 upon the cup assembly being moved to the delivery passageway 34 (see FIGS. 5 and 6). A sealing spring 120 is provided between the sled 100 and the cup 98 for biasing the medicament cup 98 against a bottom surface of the hopper 42 to seal the dispenser port 44 of the reservoir 14. The cup 98 includes clips 122 that allow the cup to be biased against the reservoir, yet retain the cup in the sled 100.

[0031] The sled 100 includes a second sealing surface 124 adapted to seal the pressure relief port 116 when the recess 102 of the cup 98 is aligned with the dispenser port 44, and an indentation 126 (see FIG. 6) adapted to unseal the pressure relief port 116 when the first sealing surface 118 is aligned with the dispenser port 44. Operation of the pressure system is discussed below.

Dose Counting System

[0032] The dose counting system 16 is mounted to the hopper 42 and includes a ribbon 128, having successive numbers or other suitable indicia printed thereon, in alignment with a transparent window 130 provided in the housing 18 (see FIG. 2). The dose counting system 16 includes a rotatable bobbin 132, an indexing spool 134 rotatable in a single direction, and the ribbon 128 rolled and received on the bobbin 132 and having a first end 127 secured to the spool 134, wherein the ribbon 128 unrolls from the bobbin 132 so that the indicia is successively displayed as the spool 134 is rotated or advanced.

[0033] The spool 134 is arranged to rotate upon movement of the yokes 66, 68 to effect delivery of a dose of medicament from the reservoir 14 into the delivery passageway 34, such that the number on the ribbon 128 is advanced to indicate that another dose has been dispensed by the inhaler 10. The ribbon 128 can be arranged such that the numbers, or other suitable indicia, increase or decrease upon rotation of the spool 134. For example, the ribbon 128 can be arranged such that the numbers, or other suitable indicia, decrease upon rotation of the spool 134 to indicate the number of doses remaining in the inhaler 10. Alternatively, the ribbon 128 can be arranged such that the numbers, or other suitable indicia, increase upon rotation of the spool 134 to indicate the number of doses dispensed by the inhaler 10.

[0034] The indexing spool 134 preferably includes radially extending teeth 136, which are engaged by a pawl 138 extending from one of the cam followers 78 (see FIGS. 3 and 11) of the second yoke 68 upon movement of the yoke to rotate, or advance, the indexing spool 134. More particularly, the pawl 138 is shaped and arranged such that it engages the teeth 136 and advances the indexing spool 134 only upon the mouthpiece 24 cover 28 being closed and the yokes 66, 68 moved back towards the cap 26 of the housing 18.

[0035] The dose counting system 16 also includes a chassis 140 that secures the dose counting system to the hopper 42 and includes shafts 142, 144 for receiving the bobbin 132 and the indexing spool 134. The bobbin shaft 142 is preferably forked and includes radially nubs 146 for creating a resilient resistance to rotation of the bobbin 132 on the shaft 142. A clutch spring 148 is received on the end of the indexing spool 134 and locked to the chassis 140 to allow rotation of the spool 134 in only a single direction (counterclockwise as shown in FIG. 14). Operation of the dose counting system 16 is discussed below.

Operation

[0036] FIG. 13 illustrates the relative movements of the boss 110 of the cup sled 100, and the ratchet 106 and the push bar 108 of the second yoke 68 as the mouthpiece cover 28 is opened and closed. In the first

position of the yokes 66, 68 (wherein the cover 28 is closed and the cam followers 78 are in contact with the first cam surfaces 90 of the cams 70), the ratchet 106 prevents the cup spring 104 from moving the cup sled 100 to the delivery passageway 34. The dose metering system is arranged such that when the yokes are in the first position, the recess 102 of the medicament cup 98 is directly aligned with the dispenser port 44 of the reservoir 14 and the pressure relief port 116 of the spacer 38 is sealed by the second sealing surface 124 of the cup sled 100.

[0037] Upon the cover 28 being partially opened such that the second cam surfaces 92 of the cams 70 engage the cam followers 78, the actuator spring 69 is allowed to move the yokes 66, 68 linearly towards the mouthpiece 24 to the second position and partially collapse the bellows 40 of the medicament reservoir 14. The partially collapsed bellows 40 pressurizes the interior of the reservoir 14 and ensures medicament dispensed from the dispenser port 44 of the reservoir fills the recess 102 of the medicament cup 98 such that a predetermined dose is provided. In the second position, however, the ratchet 106 prevents the cup sled 100 from being moved to the delivery passageway 34, such that the recess 102 of the medicament cup 98 remains aligned with the dispenser port 44 of the reservoir 14 and the pressure relief port 116 of the spacer 38 remains sealed by the second sealing surface 124 of the cup assembly 96.

[0038] Upon the cover 28 being fully opened such that the third cam surfaces 94 engage the cam followers 78, the actuator spring 69 is allowed to move the yokes 66, 68 further towards the mouthpiece 24 to the third position. When moved to the third position, the ratchet 106 disengages, or falls below the boss 110 of the cup sled 100 and allows the cup sled 100 to be moved by the cup spring 104, such that the filled recess 102 of the cup 98 is position in the venturi 36 of the delivery passageway 34 and the dispenser port 44 of the reservoir 14 is sealed by the first sealing surface 118 of the cup assembly 96. In addition, the pressure relief port 116 is uncovered by the indentation 126 in the side surface of the sled 100 to release pressure from the reservoir 14 and allow the bellows 40 to further collapse and accommodate the movement of the yokes 66, 68 to the third position. The inhaler 10 is then ready for inhalation by a patient of the dose of medicament placed in the delivery passageway 34.

[0039] As shown in FIG. 16, a breath-induced air stream 150 diverted through the delivery passageway 34 passes through the venturi 36, entrains the medicament and carries the medicament into the de-agglomerator 32 of the inhaler 10. Two other breath-induced air streams 152 (only one shown) enter the de-agglomerator 32 through the diametrically opposed inlet ports 62 and combine with the medicament entrained air stream 150 from the delivery passageway 34. The combined flows 154 and entrained dry powder medicament then travel to the outlet port 60 of the de-agglomerator and pass through the mouthpiece 24 for patient inhalation.

[0040] Once inhalation is completed, the mouthpiece cover 28 can be closed. When the cover 28 is closed, the trigger cams 70 force the yokes 66, 68 upwardly such that the first yoke 66 expands the bellows 40, and the pawl 138 of the second yoke 68 advances the indexing spool 134 of the dose counting system 16 to provide a visual indication of a dose having been dispensed. In addition, the cup assembly 96 is forced back to the first position by the pusher bar 108 of the upwardly moving second yoke 68 (see FIG. 13) such that the boss 110 of the cup sled 100 is engaged and retained by the ratchet 106 of the second yoke 68.

[0041] It should be understood that the foregoing detailed description and preferred embodiment are only illustrative of inhalers constructed in accordance with the present disclosure. Various alternatives and modifications to the presently disclosed inhalers can be devised by those skilled in the art without departing from the spirit and scope of the present disclosure. For example, the medicament cup could be provided on a rotary sled, advanced by movement of the yokes. In addition, the outlet port of the pressure relief could be provided in other locations than the side wall of the slide channel. Furthermore, the dose counting system could be adapted to provide an audible indications in addition to a visual indication of a dispensed dose. Accordingly, the present disclosure is intended to embrace all such alternatives and modifications that fall within the spirit and scope of an inhaler as recited in the appended claims.

Claims

1. A medicament inhaler (10) comprising:

a mouthpiece (24) for patient inhalation;

a delivery passageway (34) for directing an inhalation induced air flow (150) through the mouthpiece;

a channel (52) extending from the delivery passageway;

a reservoir (14) for containing medicament, the reservoir having a dispensing port (44) connected to the channel;

a cup (98) received in the channel and movable between the dispensing port and the delivery passageway;

a cup spring (104) biasing the cup towards one of the dispensing port and the passageway; and

a yoke (68) movable between at least two po-

sitions and including a ratchet (106) engaging the cup and preventing movement of the cup when the yoke is in one of the positions and allowing movement of the cup when the yoke is in another of the positions.

2. An inhaler (10) according to claim 1, wherein the cup spring (104) biases the cup (98) towards the delivery passageway (34).

3. An inhaler (10) according to either claim 1 or claim 2, wherein the yoke (68) further includes a push bar (108) adapted to return the cup (98) to the dispensing port (44) of the reservoir (14) upon movement of the yoke to one of the positions.

4. An inhaler (10) according to any one of claims 1 to 3, further comprising:

at least one movable cam (70) including at least two successive cam surfaces (90, 92, 94); and a spring (69) biasing the yoke against the cam such that movement of the cam causes the yoke to successively engage the cam surface and move the yoke between the at least two positions of the yoke.

5. An inhaler (10) according to claim 4, wherein the cam (70) includes three successive cam surfaces (90, 92, 94) for moving the yoke (68) between three positions, wherein the ratchet (106) is adapted to prevent movement of the cup (98) to the passageway when the yoke is in two of the three positions and allow movement of the cup when the yoke is in a third of the three positions, and the push bar (108) is adapted to return the cup to the dispensing port of the reservoir upon movement of the yoke to a first of the positions.

6. An inhaler (10) according to any one of claims 1 to 5, further comprising a cover (28) movable to open and close the mouthpiece (24), wherein the at least one cam (70) is secured to the cover for movement therewith, whereby opening and closing the mouthpiece causes the yoke (68) to move between the three positions (90, 92, 94) of the yoke.

7. An inhaler (10) according to any one of claims 4 to 6, wherein the cam (70) is movable by rotation.

8. An inhaler (10) according to any one of claims 1 to 7, wherein the reservoir (14) includes a volume of dry powdered medicament.

9. An inhaler (10) according to any one of claims 1 to 8, further comprising a deagglomerator (32) between the delivery passageway and the mouthpiece.

10. An inhaler (10) according to any one of claims 1 to 9, further comprising a pawl (138) extending from the yoke (68):

a dose counter (16) including,

a bobbin (132),

a rotatable spool (134),

a rolled ribbon (128) received on the bobbin and rotatable about an axis of the bobbin, the ribbon having indicia thereon successively extending between a first end (127) of the ribbon secured to the spool and a second end of the ribbon positioned on the bobbin, and

teeth (136) extending radially outwardly from the spool into a predetermined path of the pawl during movement of the yoke between the at least two positions, so that the spool is rotated by the pawl and the ribbon is advanced onto the spool during movement of the cup.

11. An inhaler (10) according to claim 10, wherein the spool (134) rotates in a single direction.

12. An inhaler (10) according to either claim 10 or 11,wherein the dose counter (16) includes a clutch spring (148) secured to the spool (134) and allowing rotation of the spool in a single direction.

13. An inhaler (10) according to any one of claims 10 to 12, wherein the indicia comprises numbers.

14. An inhaler (10) according to any one of claims 10 to 13, wherein the indicia are provided on a radially outwardly facing surface of the rolled ribbon (128).

15. An inhaler (10) according to any one of claims 10 to 14, wherein the predetermined path of pawl (138) is linear.

16. An inhaler (10) according to any one of claims 10 to 15, wherein the pawl (138) moves in first and second directions along the predetermined path and is adapted to engage the teeth (136) and advance the spool (134) upon the movement in the second direction.

17. An inhaler (10) according to any one of claims 10 to 16, further comprising a housing (18) containing the dose counter (16) include a transparent window (13) over the indicia of the ribbon.

18. An inhaler (10) according to any one of claims 10

to 17, wherein the indicia comprises numbers arranged to successively decrease as the ribbon is advanced onto the spool.

19. An inhaler (10) according to any preceding claim, wherein:

the channel (52) includes a pressure relief port (116);

a conduit provides fluid communication between an interior of the reservoir (14) and the pressure relief port; and

the cup (98) includes,

a recess (102) adapted to receive medicament when aligned with the dispensing port (44) of the reservoir,

a first sealing surface (118) adapted to seal the dispensing port when the recess is unaligned with the dispensing port; and

a second sealing surface (124) adapted to seal the pressure relief port (116) of the channel (52) when the recess is aligned with the dispensing port and unseal the pressure relief port when the recess is unaligned with the dispensing port.

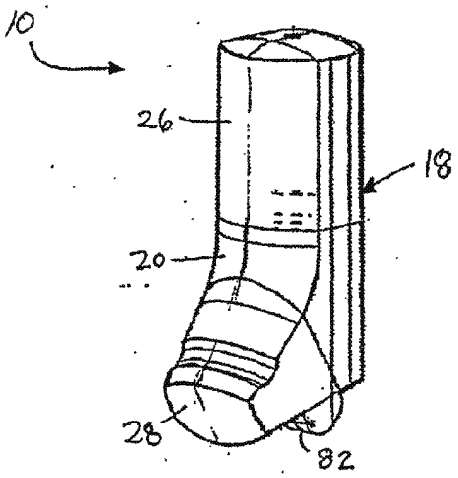

10
26
18
20
28
82

FIG. 1

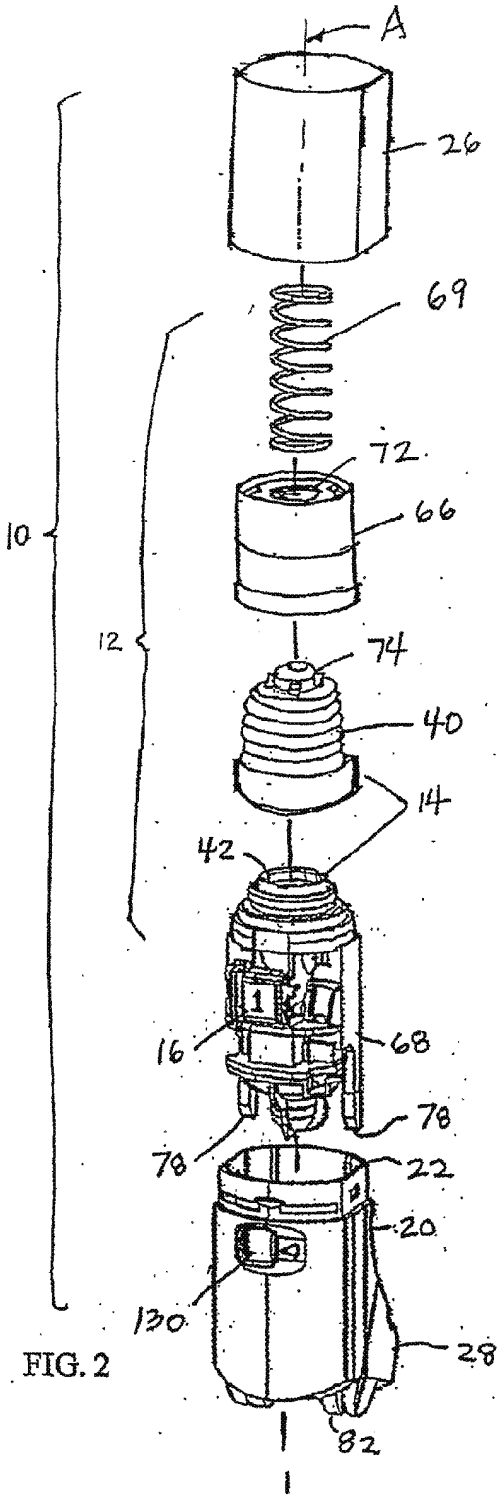

A
26
69
72
66
10
12
74
40
14
42
16
68
78
78
22
20
130
28
82
1

FIG. 2

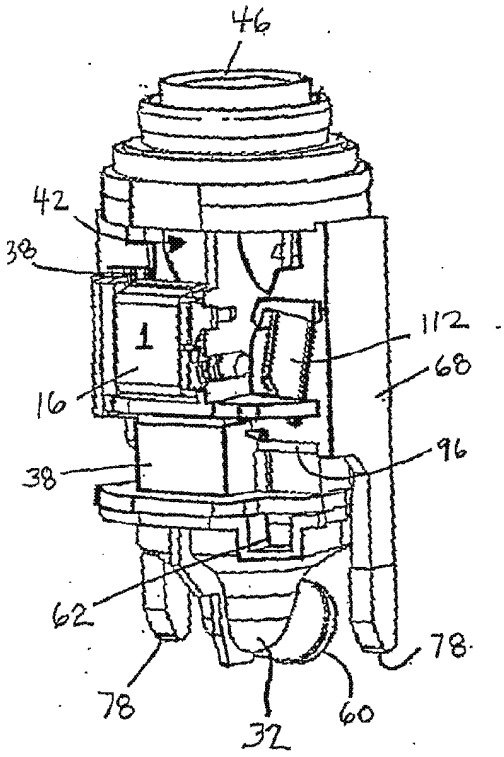


FIG. 3

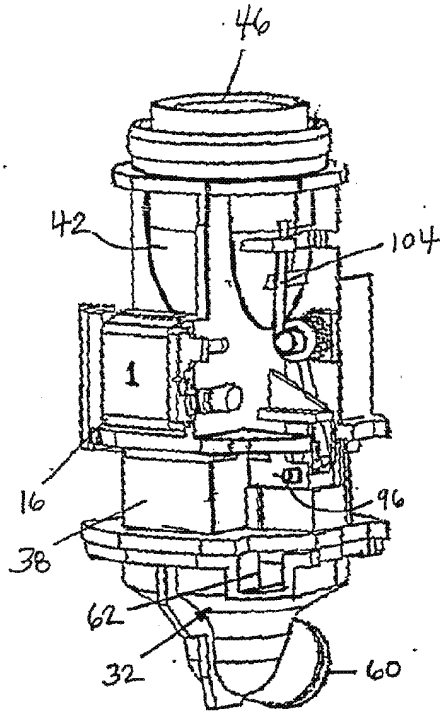


FIG. 4

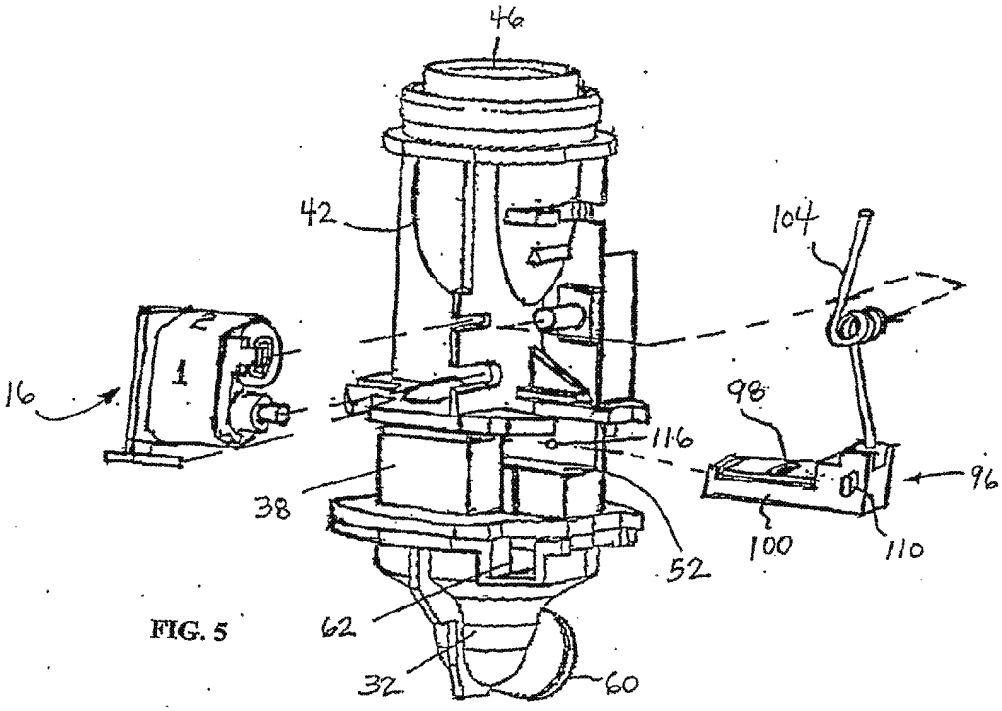

46
42
104
16
98
116
96
38
52
100
110
62
32
60

FIG. 5

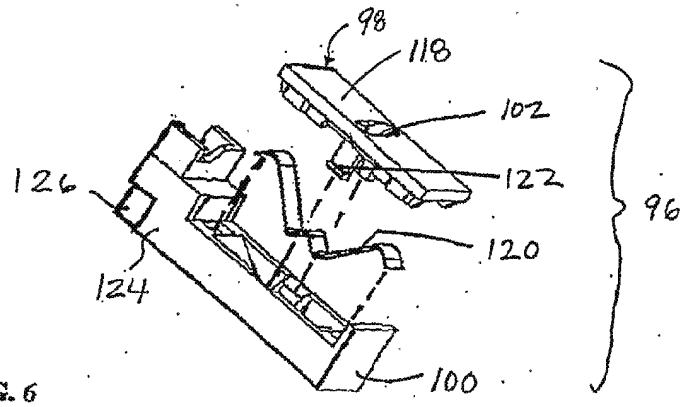

98
118
102
122
126
96
120
124
100

FIG. 6

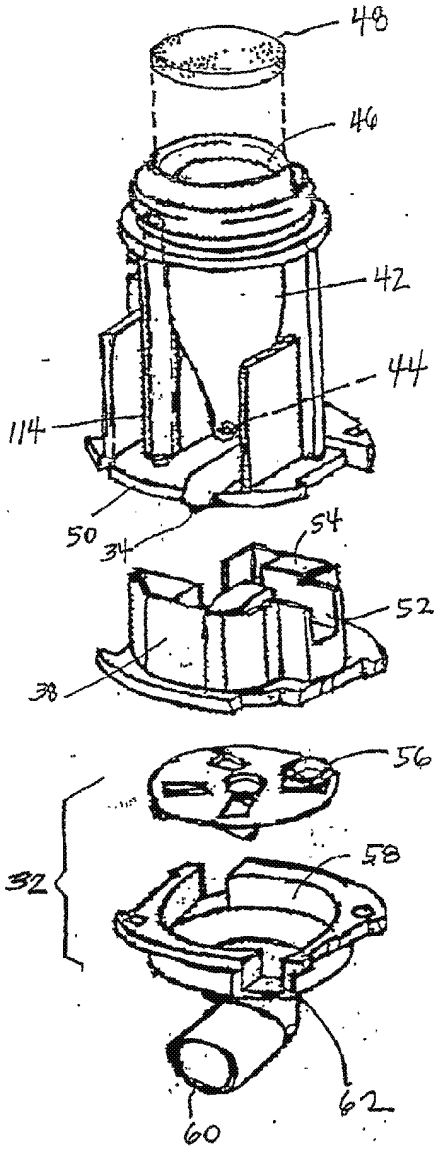

48
46
42
44
114
50
34
54
52
38
56
58
32
60
62

FIG. 7

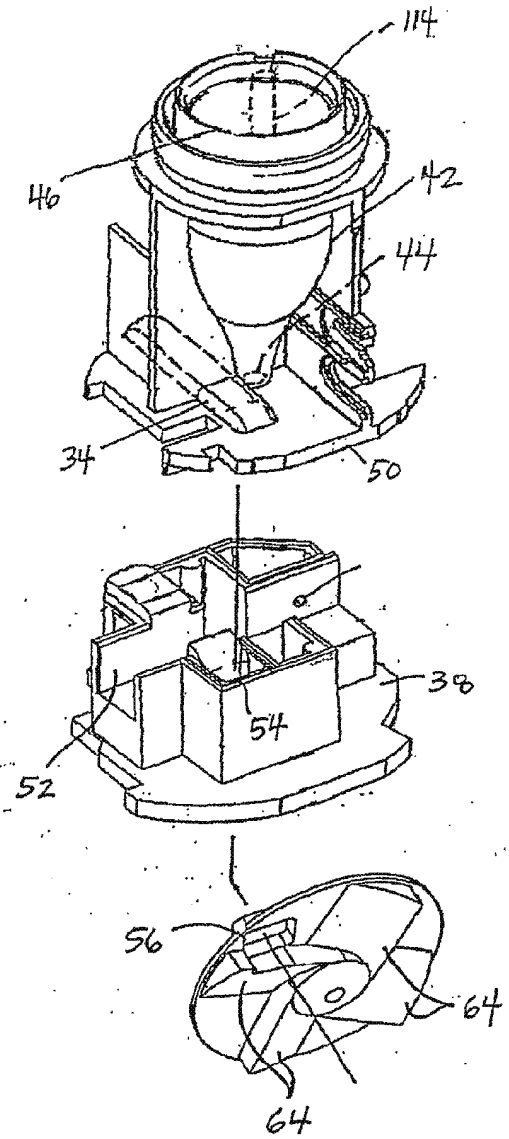

114
46
42
44
34
50
54
38
52
56
64

FIG. 8

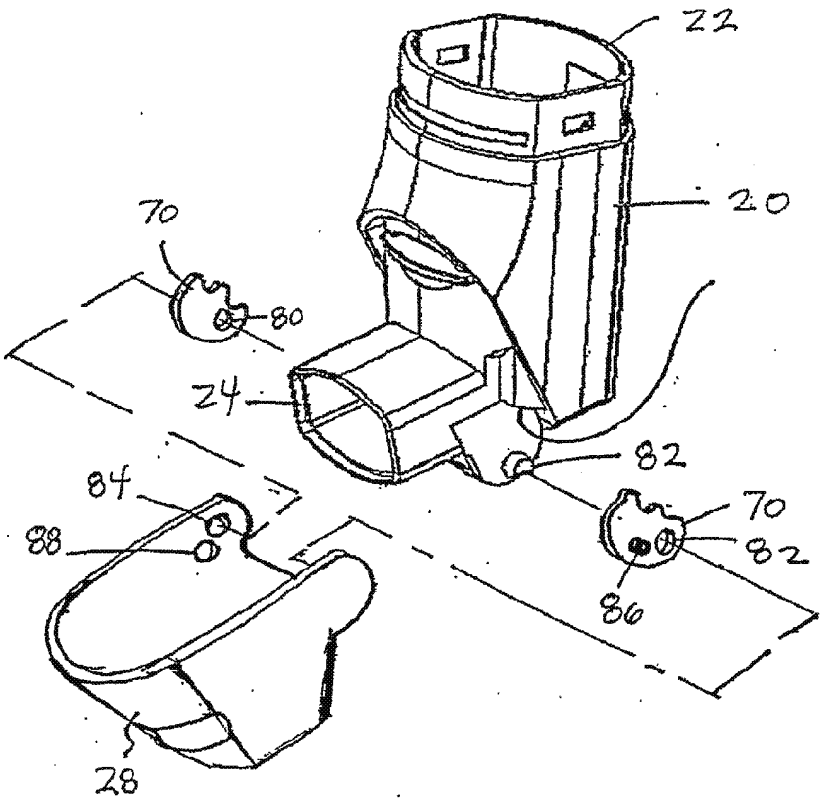


FIG. 9

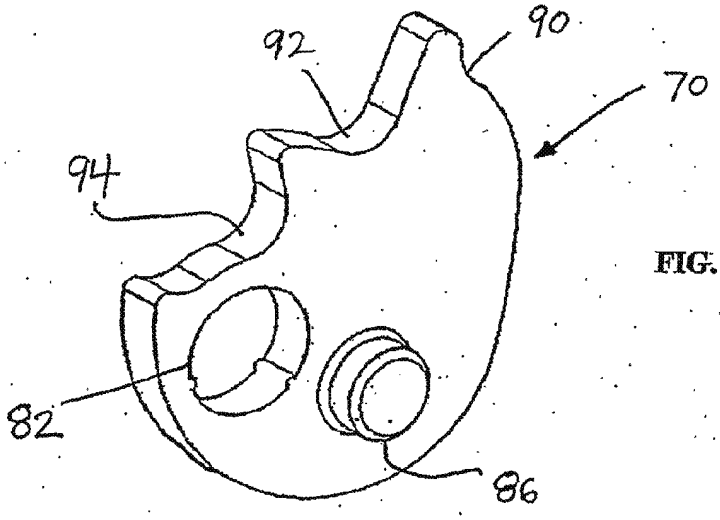


FIG. 10

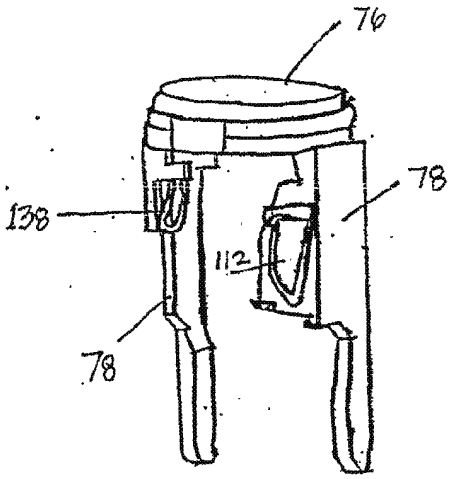


FIG. 11

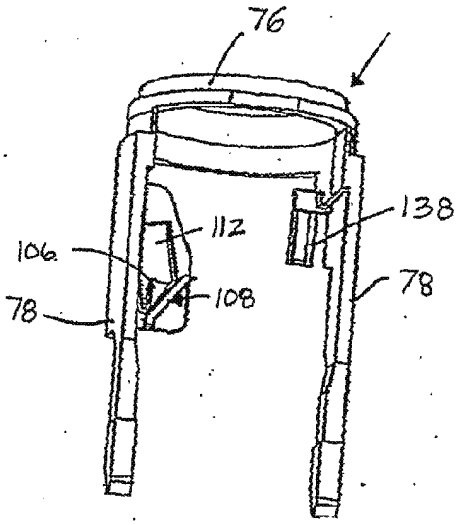


FIG. 12

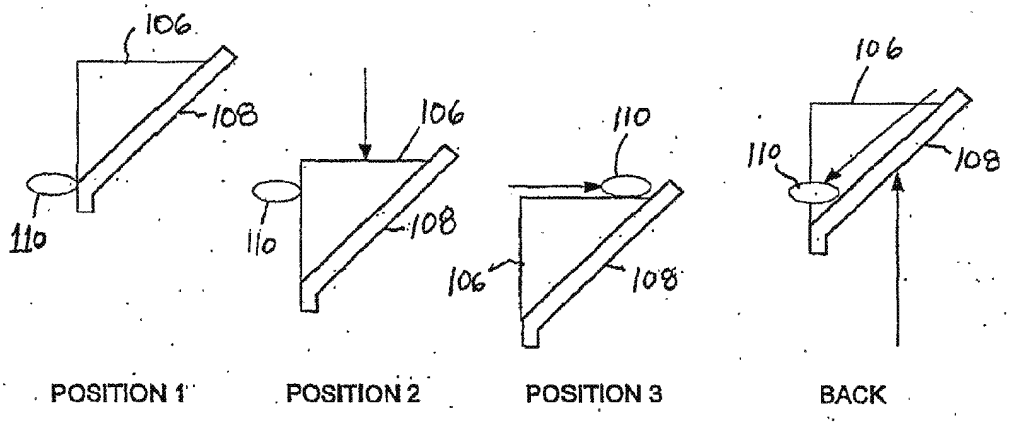


FIG. 13

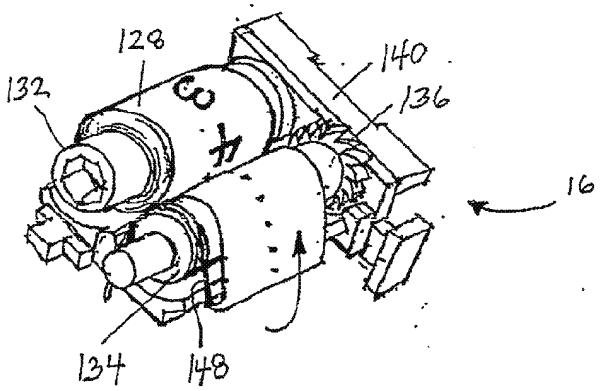


FIG. 14

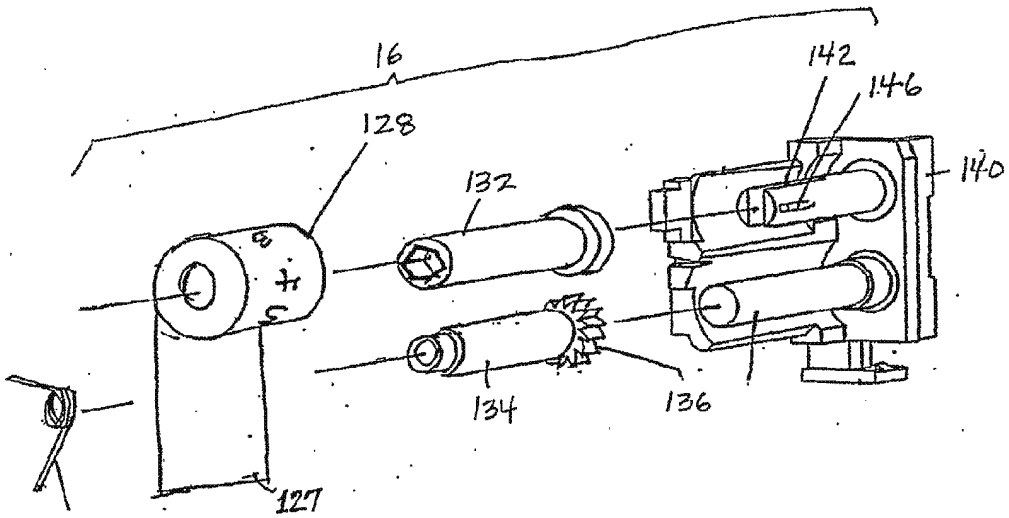


FIG. 15

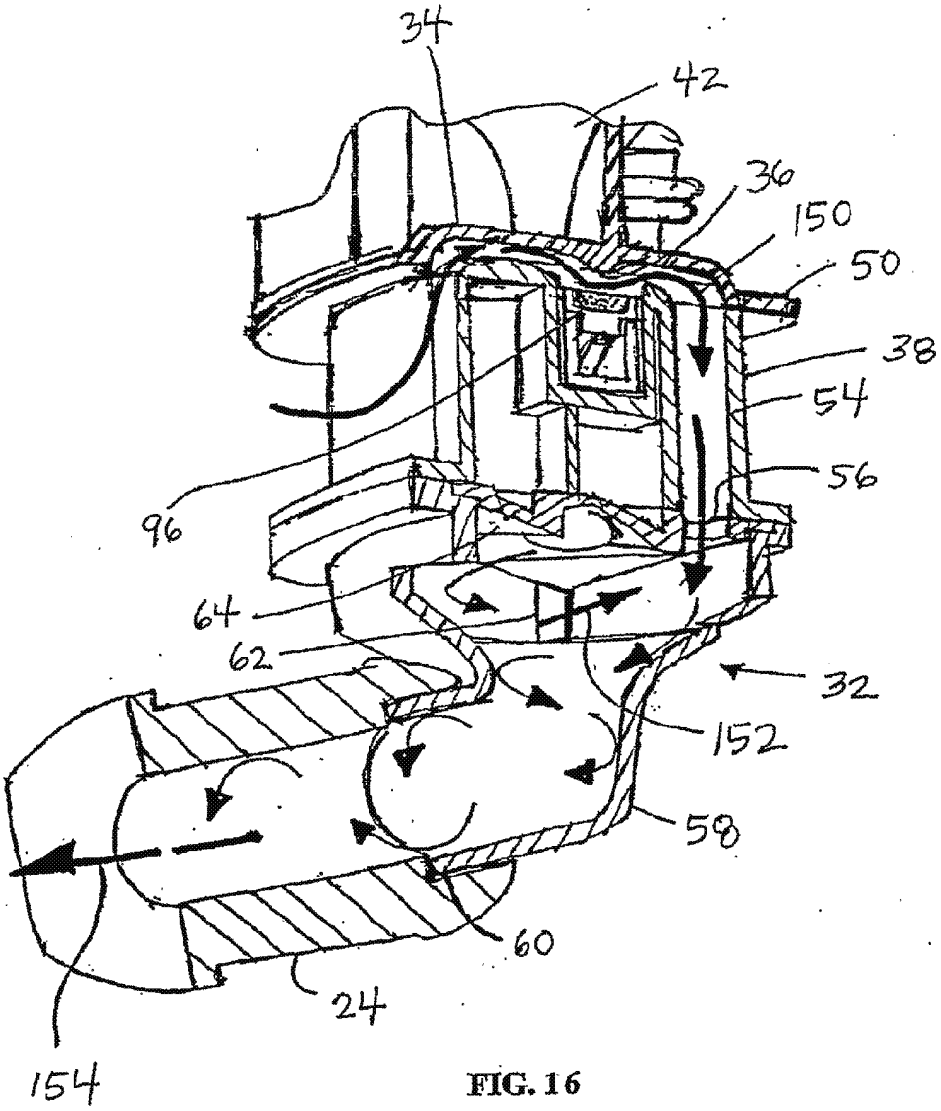


FIG. 16

EXHIBIT 11

8475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 08, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *14/103,324*
FILING DATE: *December 11, 2013*
PATENT NUMBER: *9463289*
ISSUE DATE: *October 11, 2016*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

TEVE-139US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No:	To Be Assigned
Applicant:	Declan Walsh et al.
Filed:	Herewith
Title:	DOSE COUNTERS FOR INHALERS, INHALERS AND METHODS OF ASSEMBLY THEREOF
TC/A.U.:	To Be Assigned
Examiner:	To Be Assigned

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98 and to the duty of disclosure set forth in 37 C.F.R. § 1.56, the Examiner in charge of the above-identified application is requested to consider and make of record the references listed on the PTO/SB/08a and/or PTO/SB/08b forms submitted herewith. A copy of the references listed on the PTO/SB/08a (and/or PTO/SB/08b) form is not required to be enclosed for reasons set forth below.

Although the information submitted herewith may be "material" to the Examiner's consideration of the subject application, this submission is not intended to constitute an admission that such information is "prior art" as to the claimed invention.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made.

Under 37 C.F.R. § 1.98(d), copies of the patents and publications listed on the enclosed PTO/SB/08a (and/or PTO/SB/08b) are not required to be provided, because they were cited by or submitted to the Patent and Trademark Office in prior application Serial No. 13/110,532, filed May 18, 2011, which is relied upon for an earlier filing date under 35 U.S.C. § 120.

TEVE-139US1

This Information Disclosure Statement is being filed concurrently with the above-referenced application.

Respectfully submitted,

Christopher R. Lewis, Reg. No. 36,201
Brett J. Rosen, Reg. No. 56,047
Attorneys for Applicants

CRL/BJR/mf

Enclosures: PTO/SB/08a and/or PTO/SB/08b

Dated: December 11, 2013

P.O. Box 980
Valley Forge, PA 19482-0980
(610) 407-0700

The Director is hereby authorized to charge or credit Deposit Account No. **18-0350** for any additional fees, or any underpayment or credit for overpayment in connection herewith.

2144119

PTO/SB/08a (02-09)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

SHEET 1 of 1

Complete if Known	
Application Number	To Be Assigned
Filing Date	Herewith
First Named Inventor	Declan Walsh
Art Unit	To Be Assigned
Examiner Name	To Be Assigned
Attorney Docket No.	TEVE-139US1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number - Kind Code[2] (if known)	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-6,446,627	09-10-2002	Bowman et al.	Entire Document
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3] - Number[4] - Kind Code[5] (If known)	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		EP 1486227	12-15-2004	Keane et al.	Entire Document	☐
		WO 2008119552	10-09-2008	Fenlon	Entire Document	☐
		WO 9828033	07-02-1998	Bowman et al.	Entire Document	☐
		EP 1330280	11-10-2004	Keane et al.	Entire Document	☒
						☐
						☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

[1]Applicant's unique citation designation number (optional).

[2]See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3]Enter Office that issued the document, by the two-letter code (WIPO Standard St.3).

[4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

[5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

[6]Applicant is to place a check mark here if English language translation is attached.

The collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

EXHIBIT 12

8475755

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 08, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *15/269,249*
FILING DATE: *September 19, 2016*
PATENT NUMBER: *9808587*
ISSUE DATE: *November 07, 2017*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/119552 A1

(51) International Patent Classification:
G06M 1/04 (2006.01) *G06M 1/08* (2006.01)

(21) International Application Number:
PCT/EP2008/002590

(22) International Filing Date: 1 April 2008 (01.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/921,320 2 April 2007 (02.04.2007) US
0706999.0 11 April 2007 (11.04.2007) GB

(71) Applicant *(for all designated States except US)*: **IVAX PHARMACEUTICALS IRELAND** [IE/IE]; Unit 301, Industrial Park, Waterford (IE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **FENLON, Derek** [IE/IE]; Unit 301, Industrial Park, Waterford (IE).

(74) Agent: **COTTAM, David, William**; Teva Europe Patent Department, 167 Fleet Street, London EC 4A 2EA (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** METERED-DOSE INHALER

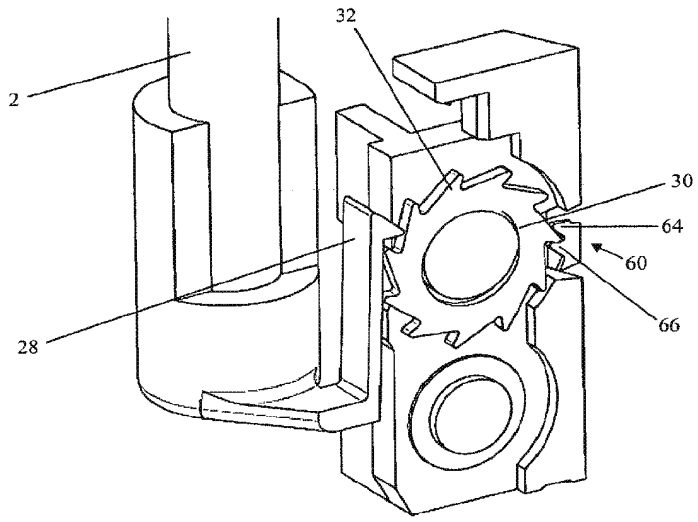


Fig. 5

(57) **Abstract:** The present invention relates to a metered dose inhaler dose counter, the counter comprising: an actuator; a rotary gear wheel having a plurality of ratchet teeth; a driver for driving the rotary gear in a step-wise fashion in response to displacement of the actuator; a pawl that prevents reverse rotation of the rotary gear; and a display coupled to the rotary gear.

WO 2008/119552 A1

Metered-dose inhaler

This invention relates to a metered-dose inhaler and in particular to a dose counter for a metered-dose inhaler, the counter comprising: an actuator; a rotary gear; a driver for driving the rotary gear in a step-wise fashion in response to displacement of the actuator, the rotary gear comprising a wheel mounted on a spindle which wheel having a plurality of ratchet teeth around its periphery; a pawl to prevent reverse rotation of the rotary gear; and a display coupled to the rotary gear, the display having a visible array of incrementing integers on a surface thereof indexable by a single integer in response to each step of the step-wise rotary motion of the rotary gear; wherein the pawl comprises at least two ratchet teeth which are radially spaced such that one of the teeth engages with the ratchet teeth of the wheel following each step of the step-wise rotary motion of the rotary gear.

Metered-dose inhalers include pressurised metered-dose inhalers (of both manually operable and breath-actuated types) and dry-powder inhalers. Such metered-dose inhalers typically comprise a medicament-containing vessel and an actuator body having a drug delivery outlet.

The medicament-containing vessel may be a pressurised canister containing a mixture of active drug and propellant. Such canisters are usually formed from a deep-drawn aluminium cup having a crimped lid which carries a metering valve assembly. The metering valve assembly is provided with a protruding valve stem which, in use, is inserted as a tight push fit into a so-called "stem block" in the actuator body.

To actuate the conventional manually operable inhaler, the user applies a compressive force to the closed end of the canister. The internal components of the metering valve assembly are spring loaded so that a compressive force of about 15 to 30 N is required to activate the device.

In response to this compressive force, the canister moves axially with respect to the valve stem by an amount varying from about 2 to 4 mm. This degree of axial movement is sufficient to actuate the metering valve and cause a metered quantity of the drug and propellant to be expelled through the valve stem. This is then released into the mouthpiece via a nozzle in the stem block. A user inhaling through the drug delivery outlet of the device at this point will thus receive a dose of the drug.

Metered-dose inhalers as described above administer an accurate dose of medicament whenever required, which is particularly useful for users whose respiratory difficulties manifest themselves suddenly. Such has been the success of these devices that they are now used throughout the world.

A more recent development is the so-called "breath-operated actuator" which delivers a dose of drug through a mouthpiece in response to inhalation by the user. This type of arrangement is particularly convenient in circumstances where the co-ordination between user inhalation and manual depression of the aerosol canister is imperfect. For example, children sometimes lack the necessary co-ordination to achieve effective self-administration and, at times of respiratory distress, adult users may also experience poor co-ordination.

One of the drawbacks of self-administration from an inhaler is that users often experience difficulty in determining when the charge in the medicament-containing vessel has nearly run out since the contents of the medicament reservoir are typically invisible to the user. With aerosol canisters, part of the reason for this difficulty is that a surplus of propellant may remain in the canister even though the drug supply is nearly exhausted. Alternatively, the near-exhausted state may result in a surplus of drug in relation to propellant. Thus, the illusion is created that the inhaler is still capable of providing useful doses of medicament simply because the canister contains liquid. This is potentially hazardous for the user since dosing becomes unreliable and because few users routinely carry a back-up device.

Many users have several different inhalers for the treatment of a variety of conditions. Others keep inhalers at a number of different locations such as at school, home, work etc. In these circumstances it is particularly difficult for the user to keep track of the amount of usage extracted from each individual inhaler apparatus.

Clearly there is a need for a counter mechanism which enables users to assess how many doses remain in the obscured canister. Such a counter would ensure that users are warned when the inhaler nears exhaustion so that appropriate measures can be taken to avoid running out of medication. Moreover, if a dose counter can provide readability to a resolution of one dose, this can be used for compliance monitoring, either under hospital supervision or by parents and teachers assessing compliance by children in their care. In addition, there are regulatory requirements for metered-dose inhalers to have a dose counter in a number of countries.

WO 98/28033 discloses a dose counter suitable for use with the above-described metered-dose inhalers. Figs 1 and 2 reproduced herein from WO 98/28033 show the lower portion of a metered-dose inhaler. The inhaler comprises an actuator body 2 having a drug delivery outlet 4. An aerosol canister 6 extends into the lower portion of the actuator 2. The aerosol canister 6 is formed from a deep-drawn aluminium cup 8 to which a lid 10 is attached by crimping.

The lid 10 carries a metering-valve assembly having a protruding valve stem 12, the end of which is received as a tight push fit in a stem block 14 of the actuator body 2. Stem block 14 has a nozzle 16 communicating with the drug delivery outlet 4 so that, upon actuation of the metering-valve assembly, a charge of the drug is emitted through the nozzle 16 into the drug delivery outlet 4. Actuation of the metering-valve assembly is effected by causing downward movement of the aerosol canister 6 relative to the actuator body 2. This may be achieved through manual pressure exerted by the user against the upturned base (not shown) of the aerosol canister 6 or by automatic depression of the aerosol canister 6 in response to user inhalation in inhalers of the breath-actuated type. The mechanism of breath actuation does not form part of WO 98/28033 or the present

invention and will not be described in further detail. A user inhaling through the drug delivery outlet 4 when the aerosol canister 6 is depressed will receive a metered dose of the drug.

A counter mechanism 18 includes an actuator 20 moulded from a plastics material, such as nylon, the actuator 20 having a boss 22 integrally formed at its base.

The underside of boss 22 is formed with a blind hole which receives a compression spring 24 mounted on an upstanding spigot 26 formed on a lower element of the counter chassis.

A driver 28 for driving a rotary gear in the form of a ratchet-toothed wheel 30 is integrally moulded with boss 22 of the actuator 20 and comprises a transverse hook element (not shown) mounted between two arms (only one visible in Fig. 2), the bases of which are conjoined to the boss 22. The transverse hook is dimensioned and oriented to engage with ratchet teeth 32 formed around the periphery of the ratchet-toothed wheel 30 to rotate it in a forward direction.

The ratchet-toothed wheel 30 is integrally moulded with a first hollow axle 34 which is rotatably supported on a first spindle 36 that projects transversely from a chassis sub-element 38. Chassis sub-element 38 also has a second spindle 40 projecting transversely therefrom on which a second hollow axle 42 is rotatably supported. A flexible tape 44 is wound around the second hollow axle 42 which serves as a supply spool and passes to the first hollow axle 34 which serves as a take-up spool (stock bobbin). A guide plate 46 forming part of the chassis sub-element 38 helps to guide the tape 44 in a smooth passage from the supply spool to the take-up spool. The surface of the tape 44 is marked with a progression of descending numbers which denote the number of doses remaining in the aerosol canister. Typically, the starting count is 200 and successive markings on the tape decrease by one. The spacing between successive markings is coincident with the indexing motion of the matching wheel 30 so that a new number appears in a window 48 provided in the inhaler housing 2 for each successive actuation.

The ratchet-toothed wheel 30 and integrally formed first hollow axle 34 are restrained from reverse rotation by a wrap-spring clutch 50 surrounding the hollow axle 34 at the end thereof remote from ratchet-toothed wheel 30. One end (not shown) of the wrap-spring clutch 50 is braced against the counter chassis. The windings of the wrap-spring clutch 50 are oriented such that rotation of the first hollow axle 34 in a forward sense is not resisted by the spring coils. However, reverse rotation of the hollow axle 34 acts so as to tighten the spring coils around it, thereby causing the first hollow axle 34 to be gripped by the internal surface of the wrap-spring clutch 50 and hence restraint from reverse rotation.

Fig. 3 shows a preferred embodiment of the invention set out in WO 98/28033. The dose counter 18 comprises an actuator 20 having a boss 22 integrally formed therewith and driver 28 joined to the boss 22. The underside of boss 22 is provided with a blind hole which receives a compression spring 24 that serves to return the actuator 20 to its rest position after depression thereof during actuation of the inhaler apparatus (not shown).

The driver 28 comprises a transverse hook 52 mounted between a pair of arms 54,56 which are joined at their bases by a web (not shown). The web is connected to the boss 22 of the actuator 20. A combined actuator and driver assembly may be integrally formed, such as from a plastics material, e.g. as nylon.

In use, the transverse hook 52 engages with ratchet teeth 32 of a ratchet-toothed wheel 30 which is mounted on a hollow axle 34 serving as a take-up spool for a flexible tape display 44. At the end of the hollow axle 34 remote from the ratchet-toothed wheel 30 is a friction clutch 50 which serves to restrain the axle 34 against reverse rotation and hence prevents reverse travel of the counter tape 44.

A control surface 58 is depicted here as a see-through element so that the workings of the dose counter may be more clearly seen. The control surface 58 extends parallel to the direction of travel of the actuator 20 and is located adjacent the ratchet-toothed wheel 30

at a position which marks a chordal projection across one of the wheel faces. One of the support arms 56 of the driver 28 is in sliding contact with control surface 58. This sliding contact serves to inhibit the natural tendency of the driver 28 to flex radially inwardly towards the axis of rotation of the ratchet-toothed wheel 30. By preventing such radially inward flexure, the control surface 58 restricts the engagement and disengagement of the drive 28 with the ratchet-toothed wheel 30 so that the distance by which the ratchet-toothed wheel 30 rotates is limited to one tooth pitch. This condition is observed regardless of the extent of linear travel, or stroke, of the actuator 20.

Fig. 4 shows a schematic view of a conventional ratchet gear and drive pawl arrangement which is used in the dose counter described in WO 98/28033. The arrangement uses a reciprocating driver 28 acting in a pushing sense to rotate a ratchet-toothed wheel 30 in the direction shown by the arrows A. A fixed pawl 60 acts to prevent reverse rotation of the ratchet-toothed wheel 30 by engagement against the trailing edge 62 of a ratchet tooth 32. However, on forward rotation of the ratchet-toothed wheel 30 in the sense of arrows A, the fixed pawl 60 is capable of radially outward deformation, urged by the leading edge 63 of a ratchet-tooth 32.

In this arrangement, if the ratchet-toothed wheel 30 is rotated by more than a single tooth pitch but by less than two tooth pitches for each reciprocating movement of the driver 28, there is a degree of reverse rotation until the pawl 60 becomes engaged by the trailing edge 62 (as opposed to the leading edge 63) of a ratchet tooth 32. Thus, the rotation of the ratchet-toothed wheel 30 may be said to be "stepped".

The components of metered-dose inhalers are manufactured to a high technical specification. However, inevitable variations in the tolerances of the components can, in some circumstances, lead to failure of the dose counter of the type disclosed in WO 98/28033. The failure of the dose counter, although not common, makes the dose counter of the type disclosed in WO 98/28033 unsuitable for some applications. There is a requirement in the art, therefore, for a dose counter with a reduced failure rate.

Accordingly, a first aspect of the present invention provides a dose counter for a metered-dose inhaler, the counter comprising:

an actuator;

a rotary gear;

a driver for driving the rotary gear in a step-wise fashion in response to displacement of the actuator, the rotary gear comprising a wheel mounted on a spindle which wheel having a plurality of ratchet teeth around its periphery;

a pawl to prevent reverse rotation of the rotary gear; and

a display coupled to the rotary gear, the display having a visible array of incrementing integers on a surface thereof indexable by a single integer in response to each step of the step-wise rotary motion of the rotary gear;

wherein the pawl comprises at least two ratchet teeth which are radially spaced such that one of the teeth engages with the ratchet teeth of the wheel following each step of the step-wise rotary motion of the rotary gear.

The counter of the present invention thus provides a pawl having at least two teeth in which one and the same tooth engages with successive ratchet teeth of the wheel during the step-wise rotary motion of the wheel to prevent reverse rotation of the wheel (and hence the rotary gear). By providing alternative positions for engaging the ratchet teeth of the wheel, the pawl increases the range of tolerances in the manufacture of the various components of the inhaler which can be accommodated. This in turn significantly reduces the failure rate of the dose counter and, in particular, the likelihood of undercounting. Clearly, undercounting is particularly undesirable as it can lead to a patient believing that there are more doses left within the inhaler than there actually are.

The present invention will now be described with reference to the accompanying drawings, in which:

Figs 1 to 4 show a dose counter for a metered-dose inhaler according to the prior art document WO 98/28033;

Fig. 5 shows elements of a dose counter according to the present invention;

Fig. 6 shows further detail of the dose counter according to the present invention;

Fig. 7 shows a schematic representation of journeys undertaken for indexing of the dose counter to occur;

Fig. 8 shows the wheel and pawl of the dose counter of the present invention in which the pawl is (a) operating from the first tooth and (b) operating from the second tooth; and

Fig. 9 shows a metered-dose inhaler containing the dose counter of the present invention.

The dose counter of the present invention is based on that set out in Figs 3 and 4 described hereinabove except that the pawl 60 has been modified. Modification of the pawl followed an in-depth study of all of the components of the inhaler. Thus, as shown in Fig. 5, the dose counter 18 of the present invention comprises an actuator 20; a rotary gear (not shown in full in Fig. 5); a driver 28 for driving the rotary gear in a step-wise fashion in response to displacement of the actuator 20, the rotary gear comprising a wheel 30 mounted on a spindle (not shown), the wheel 30 having a plurality of ratchet teeth 32 around its periphery; a pawl 60 to prevent reverse rotation of the rotary gear; and a display (not shown) coupled to the rotary gear, the display having a visible array of incrementing integers on a surface thereof indexable by a single integer in response to each step of the step-wise rotary motion of the rotary gear.

The wheel 30 has a plurality of ratchet teeth 32 and preferably has 8-14 teeth (i.e. 8, 9, 10, 11, 12, 13 or 14), more preferably 9, 10, 11 or 12 teeth, and most preferably 11 teeth. The radius of the wheel 30 measured from the centre of the wheel 30 to the tip of the teeth 32 will depend on the size of the components of the inhaler. Preferably the radius is from 1.5 to 3.5 mm, more preferably from 2.0 to 3.0 mm and most preferably 2.80 ± 0.05 mm.

As in the dose counter 18 of WO 98/28033, the dose counter 18 of the present invention preferably further comprises a control surface to regulate the position of engagement and disengagement between the driver 28 and the wheel 30. In addition, the driver 28 comprises a ratchet drive pawl and preferably the ratchet drive pawl is in the form of a straddle drive in which the element that engages the ratchet teeth of the wheel is supported between a pair of spaced apart support arms.

The pawl 60 comprises at least two ratchet teeth 64,66. Preferably, as shown in Fig. 5, the pawl 60 comprises two ratchet teeth 64,66 and no more. The at least two ratchet teeth 64,66 are radially spaced with respect to the ratchet-toothed wheel 30 such that one and the same tooth engages with the ratchet teeth 32 of the wheel following each step of the step-wise rotary motion of the rotary gear. Typically, one, and only one, of the ratchet teeth 64,66 on pawl 60 ever engages with the ratchet wheel.

Fig. 6 shows an exploded view of the dose counter 18 showing in addition to the previously described components, the stock bobbin 68 which is held taut by the action of the split hub 70. The split hub 70 avoids the need for a clutch spring as set out in WO 98/28033. Although the clutch spring could be used as an alternative or in addition to the split hub 70, in a preferred embodiment, the dose counter of the present invention does not include a clutch spring. The display is preferably an elongate counter tape 44 on which the dose count is printed or written, and more preferably the counter tape 44 is located on an indexing spool and the dose counter further comprises a stock bobbin to receive the counter tape as the indexing spool is advanced in a step-wise fashion.

In use, the operation of the dose counter 18 is as follows.

The user depresses the aerosol canister 6 which causes displacement of the actuator 20. In this embodiment, the actuator 20 is adapted to engage with the rim of the medicament canister 6. The actuator 20 is operable by linear displacement from a first position to a second position and back to the first position and movement of the rotary gear occurs either during the displacement of the actuator from the first position to the second position or during the displacement of the actuator from the second position to the first position. In the embodiment shown in Fig. 5, the movement of the rotary gear occurs during the displacement of the actuator from the first position to the second position. In the embodiment shown, the actuator 20 comprises a spring-loaded plunger 22,24, the plunger being depressible against the return force of the spring loading when the actuator is caused to deliver a dose of medicament.

During the movement from the first position to the second position, the actuator 20 causes the driver 28 to engage the trailing edge 62 of the ratchet tooth 32 of the wheel 30. As the actuator 20 and driver 28 move down the ratchet-toothed wheel 30 rotates.

The spindle of the rotary gear moves the counter tape 44 revealing the next integer. The counter tape 44 is held taut by the action of the split hub 70 on which is mounted the stock bobbin 68.

The pawl 60 radially outwardly deforms to allow the wheel 30 to rotate by one tooth 32. The at least two teeth 64,66 of pawl 60 may be inherently resilient to allow the required radially outward deformation and return. Alternatively or in addition, the pawl 60 may be mounted on a resilient support capable of radially outward deformation, for example the resilient support may be a resilient flange incorporated in to the chassis of the dose counter 18.

The driver 28 releases the ratchet-toothed wheel 30 after it has engaged with the pawl 60. On reset of the inhaler, the canister 6 is allowed to return to its initial (first) position. The compression spring 24 pushes the actuator 20 to follow the canister. The driver 28 on the actuator 20 flexes to pass over the teeth of the ratchet-toothed wheel 30 as the actuator 20 moves from the first to the second position.

The tooth of the at least two teeth 64,66 which has engaged tooth 32 of the wheel 30 prevents the rotary gear from rotating backwards.

The counter mechanism of the type described with reference to WO 98/28033 and in accordance with the present invention must rotate the wheel 30 of the rotary gear by exactly one tooth spacing each time the actuator is depressed. By tooth spacing is meant one tooth pitch, i.e. the radial distance between the same notional point two adjacent teeth 32 on the ratchet-toothed wheel 30. The stroke available for indexing the rotary gear is equal to the full stroke of the actuator 2. Where the metered-dose inhaler is a pressurised

inhaler, the stroke available for counting is equal to the full stroke of the medicament canister 6. However, there are three movements (or "journeys") that must be completed within this total distance for indexing of the dose counter to occur. The three journeys are shown schematically in Fig. 7.

Fig. 7 shows a graphical representation the amount of canister travel and the excess stroke available before the three critical journeys must occur. Firstly, the canister travel must close the start gap which is the sum of the tolerances of the manufactured components in the vertical direction. Secondly, the stroke must take up any lost motion, such as in pivot play, flexing of the pawl and arc motion of the drive pawl. Thirdly, is the so-called "stroke to count", which is the journey which leads to indexing of the rotary gear by one tooth spacing.

The stroke available for counting will clearly depend on the type of metered-dose inhaler used. By way of example, a suitable inhaler is the pressurised metered-dosed inhaler EasiBreathe® which uses a Qvar® canister. The canister stroke in this inhaler was measured as 3.04 ± 0.255 mm. This tolerance represents ± 3 standard deviations so that 99.7% of all canister strokes will lie within these limits. The measurements were taken from force versus displacement profiles for Qvar® canisters. One hundred and fifty canisters were measured at the start, middle and end of life giving a total of 450 stroke measurements.

The start gap is the tolerance stack in the vertical direction and includes a first distance between the part of the driver 28 which engages the wheel 30 and the appropriate ratchet tooth 32 of the wheel 30 of the rotary gear, and a second distance between the top of the actuator 20 and the canister 6. The tolerance in the vertical direction was found to be ± 0.47 mm. The nominal start gap for the EasiBreathe® inhaler is set at 0.85 mm and hence the start gap with tolerances is 0.85 ± 0.47 mm.

Thus, since the start gap is 0.85 ± 0.47 mm the maximum start gap (mean plus 3 standard deviations) is 1.32 mm (0.85 + 0.47). When such a start gap occurs, a short-stroking

canister (for example, 2.79 mm) will not rotate the wheel 30 of the rotary gear by a full tooth spacing. This will lead to failure of the dose counter. However, the provision of a first and second ratchet tooth 64,66 in the pawl 60 allows the ratchet tooth 32 of the wheel 30 of the rotary gear to rest on the second tooth 66. In the present embodiment, the second tooth 66 is 0.60 mm away from the first tooth 64. Thus, for the next actuation, the start gap is reduced to 0.72 mm (1.32 – 0.60). The stroke is therefore sufficient to rotate the wheel 30 a full index starting from this point. The step-wise rotation of the wheel 30 then continues with all subsequent actuations starting and finishing with the ratchet teeth 32 of the wheel 30 of the rotary gear engaged with the second tooth 66 of the pawl 60.

Fig. 8 shows a more detailed view of the wheel 30 of the rotary gear, the driver 28 and the pawl 60 to prevent reverse rotation of the rotary gear. In Fig. 8(a) the ratchet tooth 32a of the wheel 30 is engaged with the first ratchet tooth 64 of the pawl. In Fig. 8(b) the same tooth 32a of the wheel 30 is engaged with the second ratchet tooth 66 of the pawl 60. It may be seen that the start gap is reduced in the arrangement shown in Fig. 8(b) in comparison with the same distance in Fig. 8(a). The second tooth 66 of the pawl 60 therefore allows the first distance S of the start gap (the between the part of the driver 28 which engages the wheel 30 and the appropriate ratchet tooth 32 of the wheel 30) to be reduced thereby accommodating a greater tolerance in the canister stroke.

As explained hereinabove, the first and second teeth 64,66 provide different starting positions for the wheel 30 of the rotary gear to accommodate different tolerance levels in the components of the inhaler. The teeth 64,66 are therefore separated radially with respect to the wheel 30. The spacing will clearly depend on the precise nature of the components used in the inhaler and hence it would be inappropriate to provide a precise numerical value. It is clear from the mechanism, however, that the radial spacing will be less than the radial distance between adjacent teeth 32 on the wheel 30 of the rotary gear.

In the embodiments shown herein, the dose counter 18 of the present invention incorporates a pawl 60 having two teeth 64,66 and only two teeth, i.e. the pawl 60 consists essentially of two teeth 64,66. However, additional teeth could be incorporated

to provide additional precision to the start position of the wheel 30 and thus additional precision in the first distance S. For example, the pawl may have 2-6, preferably two, three or four teeth, more preferably two or three and most preferably two teeth.

In a particularly preferred embodiment of the present invention, the dose counter is adapted for a canister stroke of 3.041 ± 0.256 mm: the wheel of the rotary gear has a radius of 2.80 ± 0.05mm defined as the distance from the centre of the wheel to the tip of the teeth and 11 ratchet teeth around its periphery; and the pawl comprises two ratchet teeth only which have a radial spacing of 0.6 mm. In this embodiment, the total stroke to guarantee a count is 2.372 ± 0.115 mm. The probability of failure to count or resent due to component dimension variations (manufacturing tolerances) is less than 1 in 10 million.

The present invention further provides a metered dose inhaler 72 as shown in Fig. 9. The inhaler comprises a medicament canister 6, an actuator body 74 for receiving the canister 6 and having a medicament delivery outlet, and the dose counter as described herein. The inhaler has a window 76 for viewing the integers on the tape 44. In a preferred embodiment the actuator body 74 comprises a sump and preferably a smooth rounded sump. Typically, a rounded sump is understood to have a substantially cylindrical upper portion and a substantially hemi-spherical lower portion. Typically, smooth is understood to mean that the surface is sufficiently free of surface protrusions to the extent that during normal use medicament will not substantially adhere thereto.

In one embodiment of the invention the vessel contains a medicament in the form of an aerosol. Alternatively in another embodiment of the invention the vessel contains a medicament in the form of a dry powder.

The medicament may be any medicament that is suitable to be delivered to a patient via a metered-dose inhaler. In particular medicaments for the treatment of a wide variety of respiratory disorders are delivered in this manner including anti-allergic agents (e.g. cromoglycate, ketotifen and nedocromil), anti-inflammatory steroids (e.g.

beclomethasone dipropionate, fluticasone, budesonide, flunisolide, ciclesonide, triamcinolone acetonide and mometasone furoate); bronchodilators such as: β_2-agonists (e.g. fenoterol, formoterol, pirbuterol, reproterol, salbutamol, salmeterol and terbutaline), non-selective β-stimulants (e.g. isoprenaline), and xanthine bronchodilators (e.g. theophylline, aminophylline and choline theophyllinate); and anticholinergic agents (e.g. ipratropium bromide, oxitropium bromide and tiotropium).

A further aspect of the present invention provides the use of a pawl 60 comprising at least two ratchet teeth 64,66 for preventing miscounting in a dose counter of a metered dose inhaler 72. A still further aspect of the present invention provides the use of a pawl 60 comprising at least two ratchet teeth 64,66 for preventing undercounting in a counter of a metered dose inhaler 72.

In a preferred embodiment the counter comprises an actuator 20; a rotary gear; a driver 28 for driving the rotary gear in a step-wise fashion in response to displacement of the actuator 20, the rotary gear comprising a wheel 30 mounted on a spindle 36 which wheel 30 having a plurality of ratchet teeth 32 around its periphery; and a display 44 coupled to the rotary gear, the display having a visible array of incrementing integers on a surface thereof indexable by a single integer in response to each step of the step-wise rotary motion of the rotary gear. Preferably, the pawl 60 prevents reverse rotation of the rotary gear.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

Claims

1. A dose counter for a metered-dose inhaler, the counter comprising:
an actuator;
a rotary gear;
a driver for driving the rotary gear in a step-wise fashion in response to displacement of the actuator, the rotary gear comprising a wheel mounted on a spindle which wheel having a plurality of ratchet teeth around its periphery;
a pawl to prevent reverse rotation of the rotary gear; and
a display coupled to the rotary gear, the display having a visible array of incrementing integers on a surface thereof indexable by a single integer in response to each step of the step-wise rotary motion of the rotary gear;
wherein the pawl comprises at least two ratchet teeth which are radially spaced such that one of the teeth engages with the ratchet teeth of the wheel following each step of the step-wise rotary motion of the rotary gear.

2. A dose counter as claimed in claim 1, wherein the pawl comprises two ratchet teeth and no more.

3. A dose counter as claimed in claim 1 or 2, wherein the pawl is mounted on a resilient support.

4. A dose counter as claimed in claim 3, wherein the resilient support is a resilient flange incorporated in to the body of the dose counter.

5. A dose counter as claimed in any preceding claim, further comprising a control surface to regulate the position of engagement and disengagement between the driver and the wheel.

6. A dose counter as claimed in any preceding claim, wherein the actuator is operable by linear displacement from a first position to a second position and back to the first position and wherein movement of the rotary gear occurs either during the displacement of the

actuator from the first position to the second position or during the displacement of the actuator from the second position to the first position.

7. A dose counter as claimed in any preceding claim, wherein the actuator comprises a spring-loaded plunger, the plunger being depressible against the return force of the spring loading when the actuator is caused to deliver a dose of medicament.

8. A dose counter as claimed in any preceding claim, wherein the driver comprises a ratchet drive pawl.

9. A dose counter as claimed in claim 8, wherein the ratchet drive pawl is in the form of a straddle drive in which the element that engages the ratchet teeth of the wheel is supported between a pair of spaced apart support arms.

10. A dose counter as claimed in any preceding claim, wherein the display is an elongate counter tape on which the dose count is printed or written.

11. A dose counter as claimed in claim 10, wherein the counter tape is located on an indexing spool and the dose counter further comprises a stock bobbin to receive the counter tape as the indexing spool is advanced in a step-wise fashion.

12. A dose counter as claimed in any preceding claim, wherein the actuator is adapted to engage with the rim of a medicament canister.

13. A dose counter as claimed in any preceding claim, wherein the wheel of the rotary gear has 8-14 ratchet teeth around its periphery.

14. A dose counter as claimed in claim 13, wherein the wheel of the rotary gear has 11 ratchet teeth around its periphery.

15. A dose counter as claimed in any preceding claim, wherein the wheel of the rotary gear has a radius defined as the distance from the centre of the wheel to the tip of the

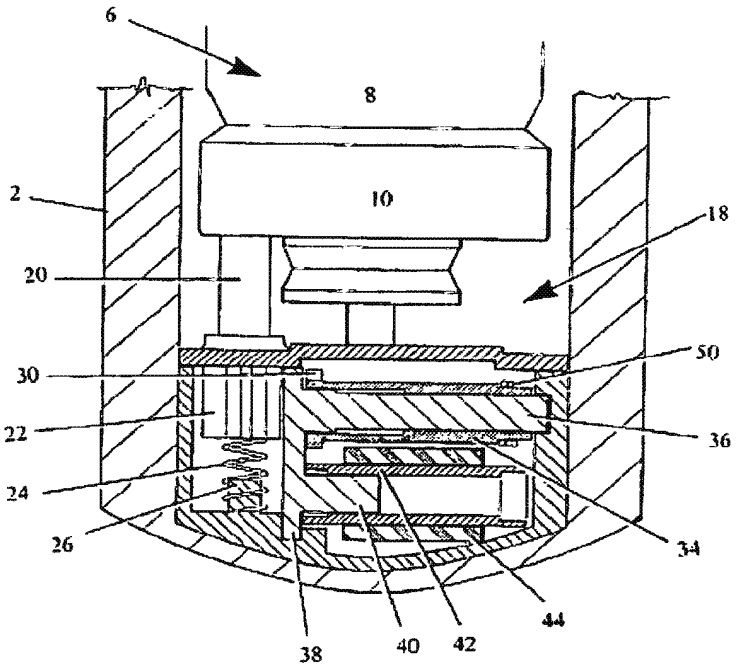
teeth of 2.80 ± 0.05 mm and 11 ratchet teeth around its periphery, and the pawl comprises two ratchet teeth and no more which have a radial spacing of 0.6 mm.

16. A metered dose inhaler comprising a medicament canister, an actuator body for receiving the canister and having a medicament delivery outlet, and the dose counter as claimed in any preceding claim.

17. A metered dose inhaler according to claim 16 wherein the actuator body comprises a smooth rounded sump.

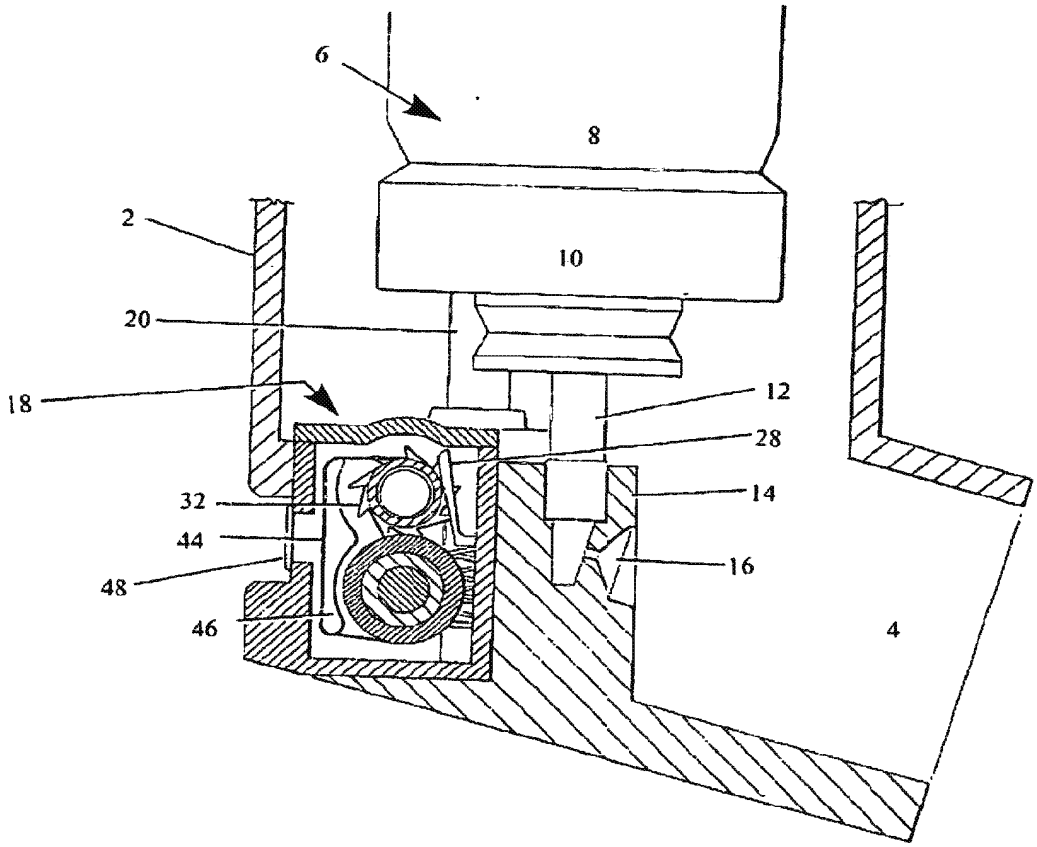
18. The use of a pawl comprising at least two ratchet teeth for preventing miscounting in a dose counter of a metered dose inhaler.

19. The use of a pawl comprising at least two ratchet teeth for preventing undercounting in a dose counter of a metered dose inhaler.



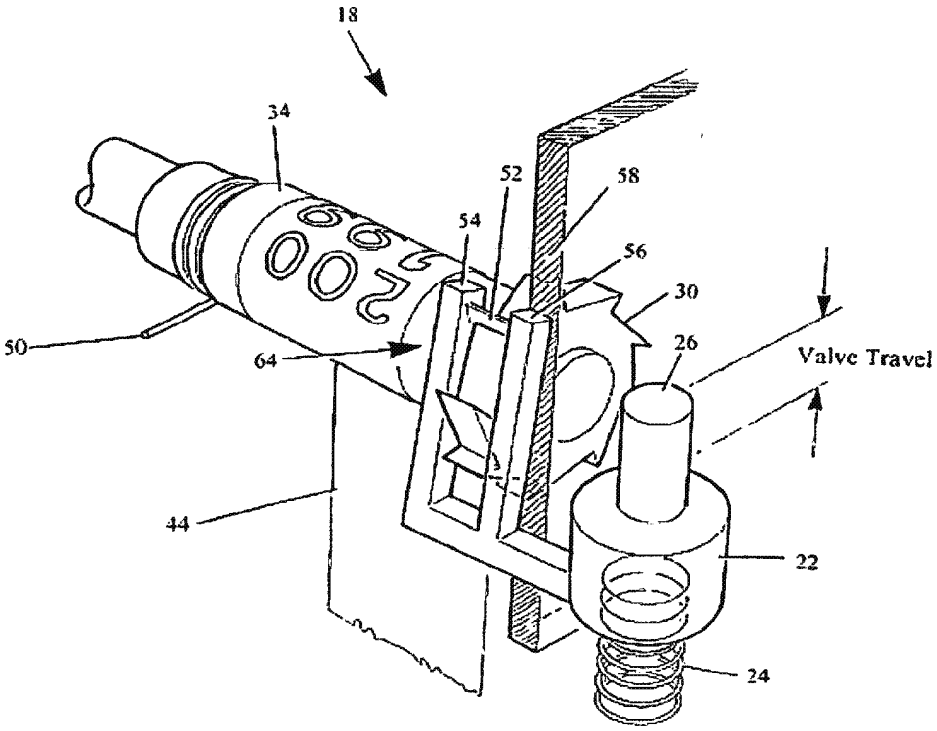
(Prior art)

Fig. 1



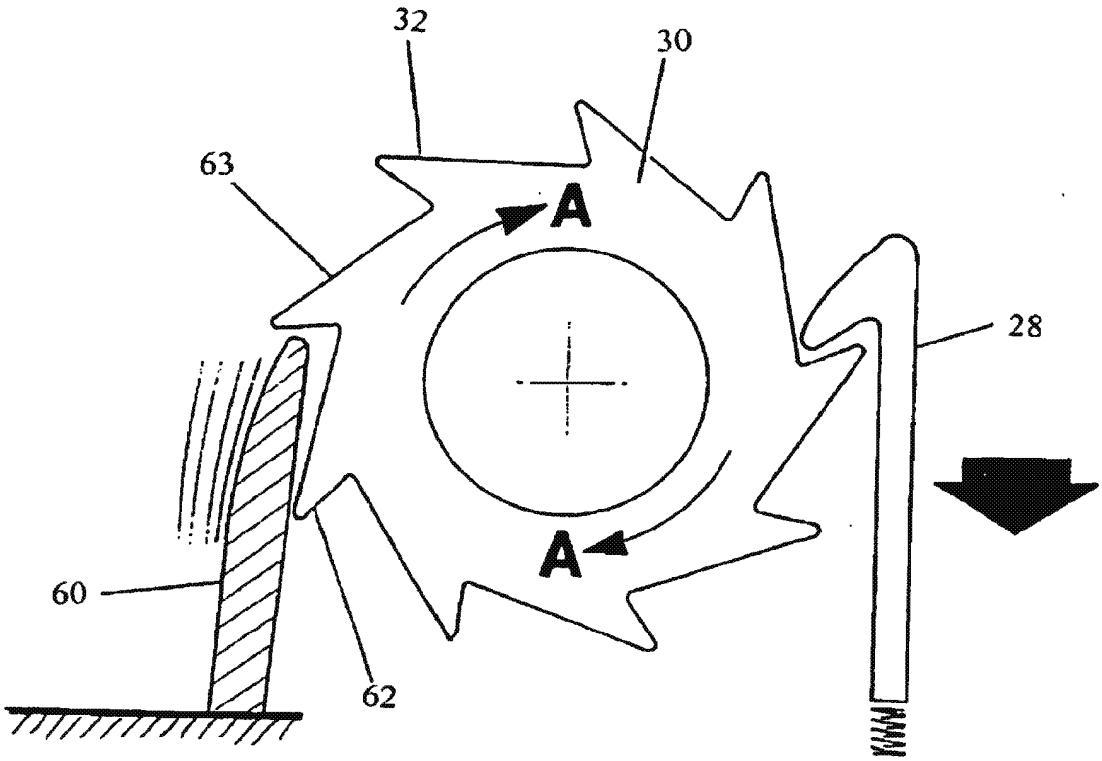
(Prior art)

Fig. 2



(Prior art)

Fig. 3



(Prior art)

Fig. 4

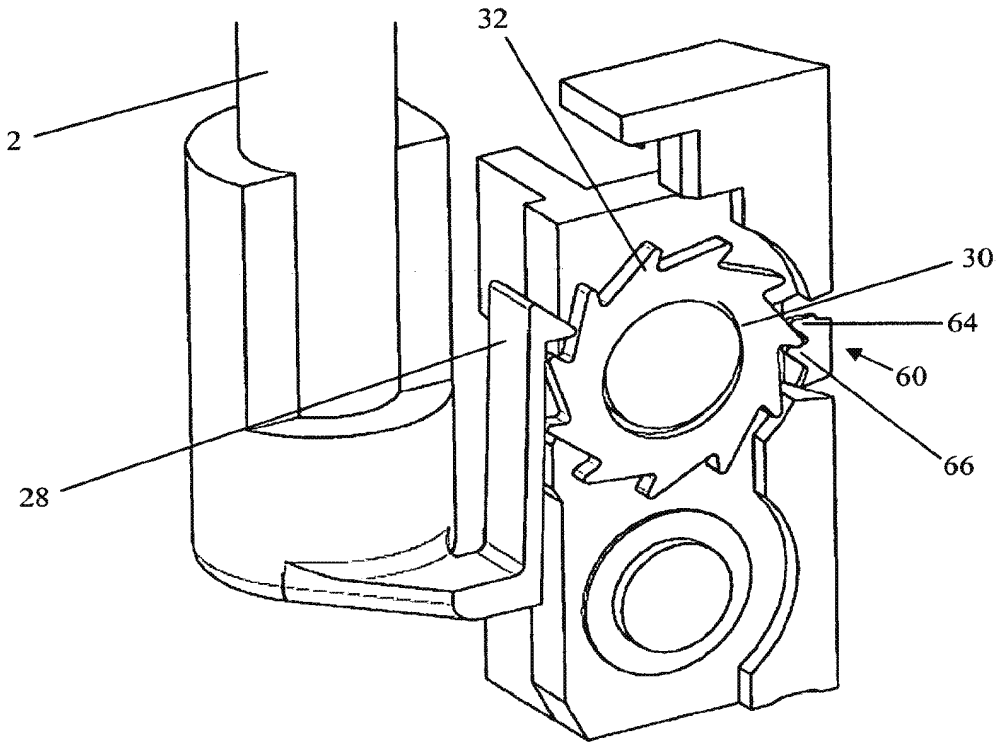


Fig. 5

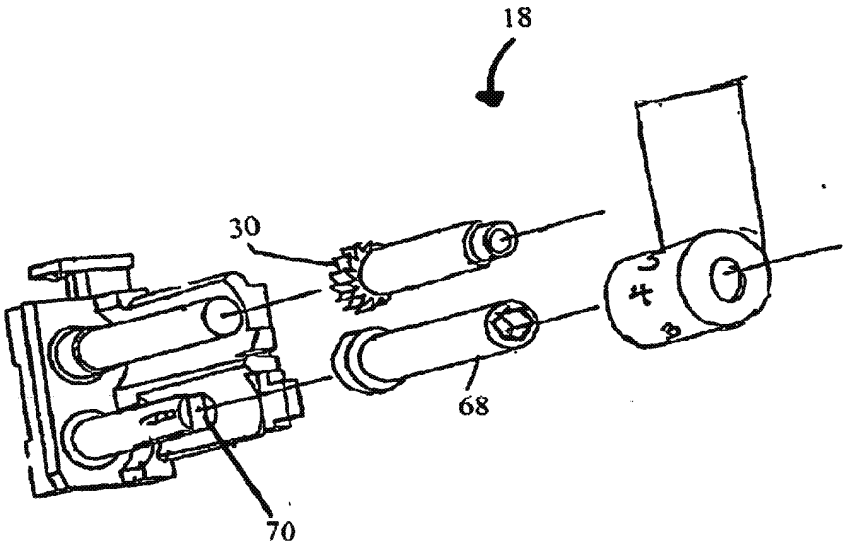

18
30
68
70

Fig. 6

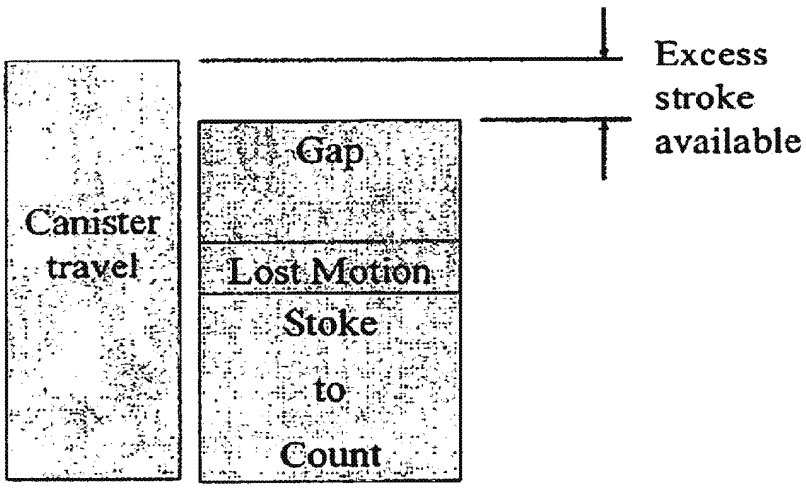

Excess
stroke
available
Canister
travel
Gap
Lost Motion
Stoke
to
Count

Fig. 7

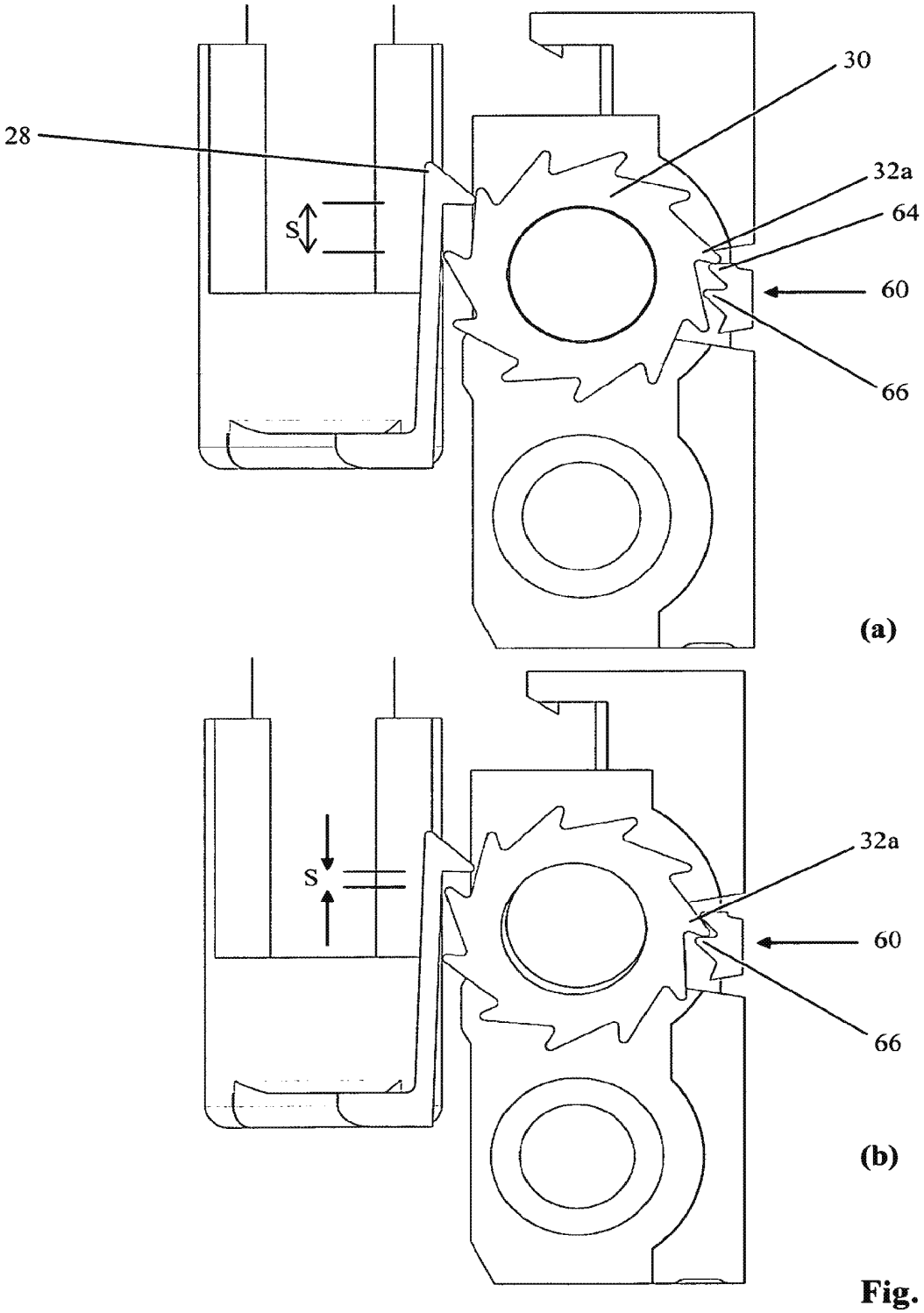


Fig. 8

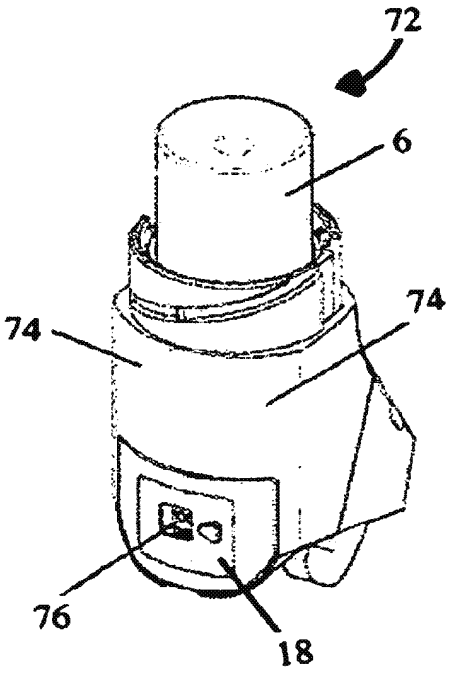


Fig. 9

EXHIBIT 13

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE

UNABRIDGED

A Merriam-Webster
REG. U.S. PAT. OFF.

Utilizing all the experience and resources of more than one hundred years of Merriam-Webster® dictionaries

EDITOR IN CHIEF
PHILIP BABCOCK GOVE, Ph.D.
AND
THE MERRIAM-WEBSTER
EDITORIAL STAFF

MERRIAM-WEBSTER INC., *Publishers*
SPRINGFIELD, MASSACHUSETTS, U.S.A.

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

Merriam-Webster™ is the name you should look for when you consider the purchase of dictionaries or other fine reference books. It carries the reputation of a company that has been publishing since 1831 and is your assurance of quality and authority.

WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY
PRINCIPAL COPYRIGHT 1961

Library of Congress Cataloging in Publication Data
Main entry under title:

Webster's third new international dictionary of the English language, unabridged: a Merriam-Webster/editor in chief, Philip Babcock Gove and the Merriam-Webster editorial staff.
p. cm.
ISBN-13: 978-0-87779-201-7 (buckram)
ISBN-10: 0-87779-201-1 (buckram)
1. English language—Dictionaries. I. Gove, Philip Babcock, 1902–1972. II. Merriam-Webster, Inc.
PE1625.W36 1993
423-dc20

MADE IN THE UNITED STATES OF AMERICA

5455QKY0605

pound as the unit of weight or mass, and the second as the unit of time — abbr. *fps*

footprint \'ˈfu̇tˌprint\ *n* **1** : an impression of the foot on a surface **2** : TRACE

foot pump *n* **1** : a portable hand pump held in place by the foot : STIRRUP PUMP **2** : a pump operated by a treadle

footrace \'ˈfu̇tˌrās\ *n* : a race run on foot

foot racer *n* : one that runs footraces

footrail \'ˈfu̇tˌrāl\ *n* **1** : a crosspiece (as between the legs of a table or chair or under a car seat) serving to support the feet **2** : the crosspiece at the foot of a bed

footrest \'ˈfu̇tˌrest\ *n* **2** a support for the feet : FOOTRAIL : FOOTSTOOL

foot-rill \'fu̇t-trəl, -üt-ˌril\ *n* [perh. alter. of *foot trail*] *Brit* : a level or inclined road giving entrance (as by a tunnel driven in a hillside) to a mine

footrope \'ˈfu̇tˌrōp\ *n* **1** : a rope rigged below a yard for men to stand on when reefing or furling — see SHIP illustration **2** : the part of a boltrope sewed to the lower edge of a sail

foot rot *n* **1 a** : a disease (as mal di gomma of citrus) that rots the stem or trunk of an affected plant near the ground **b** : a disease of cereals (as wheat) in which the culm blackens and decays resulting in lodging — compare TAKE-ALL **2** : a progressive inflammation of the tissues in the region of the feet (as between the digits) of sheep or cattle; *specif* : a necrobacillosis marked by sloughing, ulceration, suppuration, and sometimes loss of the hoof — called also *foul-foot*

foot rule *n* : a stick one foot long for measuring length or distance ⟨carpenter with *foot rule*, notebook, and pencil —May Sinclair⟩; *broadly* : a standard of measurement or judgment ⟨measured with the *foot rule* of the individual life —S.A. Coblentz⟩

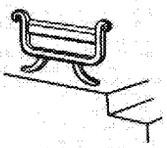
foots \'fu̇ts\ *pl of* FOOT

foot scab *n* : CHORIOPTIC MANGE

footscald \'ˈfu̇tˌskȯld\ *n* : an injury (as from a hot shoe) to the sole of a horse's foot

foot score *n* : a line 12 feet behind the tee and at right angles to the length of a curling rink from which a player delivers his stone — called also *foot line*; see CURLING illustration

footscraper \'ˈfu̇tˌskrāpər\ *n* : a sharp-edged plate or bar fixed on a doorstep for cleaning mud from the shoes before entering the house



footscraper

foot screw *n* : an adjusting screw (as on a table leg) that serves also as a foot

foot-sie \'fu̇t-sē, -sī\ *also* **foot-ie** \-ud-ē, -ət-ē, -ī\ *n* -S [fr. baby-talk dim. of *'foot*] *slang* : an action of flirting or becoming friendly or intimate often with covertness and sometimes with duplicity — usu. used with the verb *play* ⟨play ~ under the table⟩ ⟨if she was playing ~ with somebody else, how'd she find the opportunity for it —Bob Wicks⟩

foot-slog \'ˈfu̇tˌslȯg\ *vi* : to march or tramp toilsomely through or as if through mud

foot-slog-ger \'ˈfu̇tˌslȯgər\ *n* : INFANTRYMAN

foot soldier *n* : a soldier who marches and fights on foot : INFANTRYMAN

footsore \'ˈfu̇tˌsō(ə)r, -ȯ(ə)r\ *adj* : having sore or tender feet (as by reason of much walking) — **footsoreness** *n* -ES

footstalk \'ˈfu̇tˌstȯk\ *n* **1 a** : PETIOLE 1 **b** : PEDUNCLE **2** : the lower part of a millstone spindle

footstall \'ˈfu̇tˌstȯl\ *n* **1** : the stirrup of a side saddle **2** : the plinth, base, or pedestal of a pillar

footstep \'ˈfu̇tˌstep\ *n* [ME *fotstep*, *footstep*, fr. *fot*, *foot* + *step*] **1 a** : STEPPING, FOOTFALL, TREAD **b** : distance covered by a step : PACE **2 a** : the mark of the foot : TRACK **b** : TRACE, TOKEN ⟨the ~s of divine wisdom⟩ **3** : a step on which to ascend or descend ⟨~ of a carriage⟩ **4** *or* **footstep bearing** : STEP BEARING

footstick \'ˈfu̇tˌstik\ *n* : a wooden or iron stick that when wedged with quoins secures the foot of a locked-up type page

footstock \'ˈfu̇tˌstäk\ *n* : TAILSTOCK

footstone \'ˈfu̇tˌstōn\ *n* **1** : a single stone forming a kneeler at the foot of a gable slope to resist the thrust of the coping stones above **2** : a stone placed at the foot of a grave

footstool \'ˈfu̇tˌstül\ *n* **1** : a low stool to support the feet : OTTOMAN **2** : a portable step (as for mounting a horse)

foot stove *n* : a box with a pan for hot coals to warm the feet

foot switch *n* : an electric switch operated by pressure of the foot

foot tender *n* : BOTTOMER c

foot-ton \'ˈfu̇tˌtən\ *n, pl* **foot-tons** : a unit of energy equal to the work done in raising one ton against standard gravity through the height of one foot

foot up *vt* [*'foot*] : to make a total of (as the cost) ~ *vi* : to amount to when added or reckoned — usu. used with *to* ⟨his debts *foot up* to a huge sum⟩

foot-up \'ˈfu̇tˌəp\ *n* -S [*'foot*] : a lifting of the foot by a scrummager in rugby before the ball is fairly in the scrummage

foot valve *n* : a check valve at the lower end of a suction pipe (as in a well)

foot waling *n* : the inside bottom planks of a ship

footwalk \'ˈfu̇tˌwȯk\ *n* **1** : a surface paved or constructed for walking along often with a handrail (as on a bridge or on a parapet) **2** : SIDEWALK

footwall \'ˈfu̇tˌwȯl\ *n* **1** : the lower or underlying wall of a vein, ore deposit, or coal seam in a mine : the wall upon which a miner stands **2** : the lower wall of an inclined fault; *also* : the entire mass of rock below an inclined fault — opposed to *hanging wall*

foot warmer *n* **1** : a contrivance to keep the feet warm **2** : a warm covering (as a lined slipper) for the foot

foot washing *n* : a ceremonial cleansing of the feet preparatory to worship

footway \'ˈfu̇tˌwā\ *n* [ME *fotewey*, fr. *fot*, *foot* + *wey* — more at FOOT, WAY] : a footpath, sidewalk, or any way reserved for pedestrians

footwear \'ˈfu̇tˌwa(ə)r, -ˌwe(ə)r\ *n* : wearing apparel for the feet (as shoes, boots, slippers, overshoes) usu. excluding hosiery

footwell \'ˈfu̇tˌwel\ *n* : a shallow well in the afterdeck of a sailboat

footwork \'ˈfu̇tˌwərk\ *n* **1** : the management of the feet and work done with them (as in boxing, football, tennis, dancing) **2** : the activity of moving from place to place in the fulfillment of a task or purpose; *esp* : the activity of a news reporter in gathering news by direct investigation

foo-ty \'fu̇d-ē, 'fü-\ *adj* [F *foutu*, fr. past part. of *foutre* to copulate — more at FOUTER] **1** *chiefly dial* : INSIGNIFICANT, PALTRY ⟨a ~ little town⟩ **2** *chiefly dial* : poorly kept : SHODDY ⟨a pair of ~ old boots⟩

foo yong \'fu̇ 'yȯŋ, -'yəŋ\ *n* -S [Chin (Pek) *fu⁴ yung²*, lit., hibiscus] : a Chinese omelet made with bean sprouts, green pepper, and onion and fried in deep fat

¹foo-zle \'füzəl\ *vt* **foozled**; **foozled**; **foozling** \-z(ə)liŋ\ **foozles** [perh. fr. G dial. *fuseln* to work hurriedly or poorly] : to manage awkwardly : treat or play unskillfully : BUNGLE

²foozle \'' *n* -S : act of foozling; *esp* : a bungling stroke (as in golf)

foo-zler \-z(ə)lə(r)\ *n* -S : one that foozles : BUNGLER

¹fop \'fäp\ *n* -S [ME *foppe*, *fop*; akin to ME *fobben* to deceive, cheat, MHG (Alemannic dial.) *voppen*] **1** *obs* : a foolish or silly person : a conceited pretender to wit or accomplishments **2** : a man who is devoted to or vain of the exquisiteness or showiness of his dress : COXCOMB, DANDY, DUDE

²fop *vt* **fopped**; **fopped**; **fopping**; **fops** *obs* : FOOL, DUPE, CHEAT

fop-ling \'fäpliŋ\ *n* -S [*¹fop* + *-ling*] *archaic* : an insignificant or absurd man of fashion : PETIT MAÎTRE, LADIES' MAN

fop-pery \'fäp(ə)rē, -ri\ *n* -ES [*¹fop* + *-ery*] **1** : foolish character or action : FOLLY, ABSURDITY, VANITY ⟨let not the sound of shallow ~ enter my sober house —Shak.⟩ **2** : the behavior, dress, or other mark of a fop : COXCOMBRY, AFFECTATION

fop-pish \'fäpish, -pēsh\ *adj* **1** *obs* : FOOLISH, SILLY, STUPID **2** : characteristic of a fop in dress or manners ⟨a ~ embroidered nightshirt —A. Conan Doyle⟩ — **fop-pish-ly** *adv* — **fop-pish-ness** *n* -ES

fop-py \'fäpē, -pi\ *adj* -ER/-EST : FOPPISH

fop's alley *n* : a fashionable promenade (as the passage through the center of the pit) in an 18th century theater or opera house

FOQ *abbr* free on quay

¹for \fə(r), (ˌ)fȯ(ə)r, (ˌ)fō(ə), *in R speech in the southern US also* (ˌ)fär\ *prep* [ME, fr. OE; akin to OHG *fora* before, *furi* before, for, ON *fyr*, Goth *faur* before, for, L *per* through, *pro* before, for, *prae* before, Gk *pro* before, ahead, Skt *pra-* before, forward, OE *faran* to travel, go — more at FARE] **1** *obs* : BEFORE **2 a** : as a preparation toward ⟨dressing ~ dinner⟩ or against ⟨storing nuts ~ the winter⟩ or in view of ⟨making plans ~ retirement⟩ ⟨studying ~ examinations⟩ : having as goal or object ⟨volunteered ~ the air force⟩ **b** : in order to be, become, or serve as ⟨originally built ~ a church⟩ ⟨ordered eggs ~ breakfast⟩ **c** : in order to bring about or further ⟨working ~ the good of humanity⟩ **d** : to supply the need of ⟨food ~ hungry mouths⟩ **e** : with the purpose or object of ⟨an instrument ~ measuring speed⟩ **f** : adapted to ⟨suits ~ tall men⟩ ⟨a calendar ~ 1960⟩ or prerequisite to ⟨a shelf ~ books⟩ ⟨mathematics ~ engineers⟩ **g** : in order to obtain ⟨write ~ a free catalog⟩ or gain ⟨work ~ a living⟩ **h** : in order to save ⟨something in danger⟩ ⟨on trial ~ his life⟩ ⟨could not tell ~ the life of me whether he was serious⟩ ⟨running ~ dear life⟩ or to remedy ⟨take something ~ his cough⟩ ⟨don't like to sell the house, but there is nothing else ~ it⟩ ⟨mud is good ~ bee stings⟩ **3 a** — used as a function word to indicate the object of a feeling ⟨hungry ~ praise⟩ ⟨longing ~ home⟩ or faculty ⟨a taste ~ spicy food⟩ ⟨an eye ~ color⟩ **b** : so as to secure as a result : conducive to ⟨telling you ~ your own good⟩ ⟨acting ~ the best in forbidding the trip⟩ **c** (1) : intending to go to or toward ⟨has just left ~ the office⟩ ⟨starting out ~ a trip across the country⟩ (2) : on the point of : having the intention of ⟨was just ~ going to bed⟩ ⟨wise men will have it that he meant these islands, and I am not ~ arguing the point —Norman Douglas⟩ **d** — used as a function word to indicate the person or thing that something is to be delivered to ⟨any letters ~ me⟩ or assigned to ⟨a slot ~ out-of-town mail⟩ or used by or in connection with ⟨are these the tires ~ this car⟩ **4** : to the amount of ⟨a check ~ $100⟩ or extent of ⟨can see ~ miles from the hilltop⟩ or duration of ⟨waited ~ several hours⟩ ⟨won't be here ~ long⟩ or value of ⟨now pull ~ all you are worth⟩ **5 a** : in place of ⟨go to the store ~ me⟩ ⟨Doc now batting ~ Roe⟩ : in exchange as the equivalent of ⟨all that trouble ~ nothing⟩ ⟨my kingdom ~ a horse —Shak.⟩ or in requital of ⟨he gave blow ~ blow⟩ ⟨an eye ~ an eye⟩ **b** : in behalf of ⟨his lawyer will act ~ him in this affair⟩ : in support of ⟨let me carry that ~ you⟩ or in defense of ⟨fighting ~ their country⟩ : in favor of ⟨a prayer ~ those at sea⟩ ⟨which candidate are you ~⟩ — opposed to *against* **c** : in honor of : AFTER (named ~ his grandfather) **6 a** — used with a noun or pronoun followed by an infinitive to form an equivalent to such noun clauses as *that he should*, *that he might* ⟨~ him to confess would be painful⟩ ⟨shouted the news ~ all to hear⟩ ⟨~ you to have to pay for this is not fair⟩ ⟨here are some books ~ you to read⟩ **b** — used chiefly South & Midland redundantly after such verbs as *like*, *want*, *choose* ⟨I'd like ~ you to go⟩ **c** — used as a function word to introduce exclamations ⟨~ her to talk to her father like that⟩ or mild oaths ⟨~ God's sake hold your tongue and let me love —John Donne⟩ **7 a** : as being ⟨know ~ a fact⟩ ⟨do you take me ~ a fool⟩ ⟨take ~ granted⟩ ⟨mere noisy shouting often passes ~ comedy⟩ ⟨left ~ dead on the field⟩ **b** — used as a function word to indicate parenthetically an actual or implied enumeration or selection from an aggregate or series ⟨~ one thing, we have no money; ~ another, we have no time⟩ ⟨people don't buy it because, ~ one thing, the price is too high⟩ ⟨I ~ one will vote for him⟩ ⟨~ the last time, will you stop that noise⟩ ⟨be sensible ~ once⟩ **8 a** : because of ⟨shouted ~ joy⟩ : on account of ⟨decorated ~ bravery⟩ ⟨do it ~ my sake⟩ **b** *obs* : in order to prevent : for fear of ⟨here they shall not lie, ~ catching cold —Shak.⟩ **9** — used as a function word to indicate equality or proportion between numbers or quantities that are related, compared, or contrasted ⟨~ every good writer there are a dozen scribblers⟩ ⟨answered his argument point ~ point⟩ ⟨repeated the speech word ~ word⟩ ⟨the best fighter, weight ~ weight, in the country⟩ **10 a** : as regards : in respect to : CONCERNING ⟨a stickler ~ detail⟩ ⟨so much ~ that topic⟩ ⟨true ~ all I know⟩ ⟨safe ~ the present⟩ ⟨good country ~ deer⟩ **b** : in proportion to ⟨tall ~ his age⟩ : taking into account : CONSIDERING ⟨very cool ~ May⟩ ⟨that was a good score ~ him⟩ **c** : in spite of : NOTWITHSTANDING — usu. used with *all* ⟨you don't convince me ~ all your clever arguments⟩ ⟨the elephants ~ all their great size moved absolutely noiselessly —Jule Mannix⟩ ⟨a man's a man ~ a' that —Robert Burns⟩ — **for all me** : as far as I am concerned — **for all the world** — used to emphasize a likeness ⟨looked *for all the world* like a ship that had lost her foremast —Frank Yerby⟩ — **for itself** 1 *of a being* : capable of functioning esp. in the epistemological process purely by relation to itself : SELF-DETERMINED **2** *of a notion* : related to itself or its own manifestations

²for \'' *conj* [ME, fr. *for*, prep.] **1** *archaic* : by reason that : for the reason that : BECAUSE ⟨my foolish rival, that her father likes only ~ his possessions are so huge —Shak.⟩ **2** : for this reason or on this ground : as indicated or shown by the following circumstance : in substantiation of which : witness the fact that — used to introduce a reason for something before advanced (as a cause, motive, explanation, justification, or proof, of an action related or a statement made) ⟨we believe that he will succeed, ~ he has talent⟩ ⟨the army should be reduced in numbers, ~ possession of large armies has led nations to war⟩ **3** *obs* : in order that ⟨and, ~ the time shall not seem tedious, I'll tell thee what befell me —Shak.⟩

³for \'fō(ə)r, 'fō(ə), *in R speech in the southern US also* 'fär\ *n* -S [*'for*] **1** : one who takes the affirmative side **2** : what is said or felt in favor of someone or something : PRO

for- *prefix* [ME, fr. OE; akin to OHG *fir-*, *far-*, *fur-* for-, OS *for-*, Goth *fra-*, *fair-* for-, *faur-* for-, fore-, OE *for*] **1** : so as to involve prohibition, exclusion, omission, failure, or refusal — almost exclusively in words coined before 1600 ⟨*for*say⟩ ⟨*for*heed⟩ **2** : destructively or detrimentally — almost exclusively in words coined before 1600 ⟨*for*hang⟩ ⟨*for*storm⟩ **3** : completely : excessively : to exhaustion : to pieces — almost exclusively in words coined before 1600 ⟨*for*bruise⟩ ⟨*for*weary⟩ ⟨*for*spent⟩

for *abbr* **1** foreign **2** forel **3** forest; forestry

FOR *abbr* free on rail

fora *pl of* FORUM

for a' \fə'rȯ\ *adv, Scot* : NEVERTHELESS, NOTWITHSTANDING ⟨she has a bonny face for a'⟩

¹for-age \'fȯrij, 'fär-, -ēj\ *n* -S *often attrib* [ME, fr. MF *fourage*, *forage*, fr. OF, fr. *forre*, *fuerre* fodder, straw, of Gmc origin; akin to OHG *fuotar* food, fodder — more at FOOD] **1 a** : vegetable food (as hay, grain) for domestic animals (~ crop) **b** : food that wild or domestic animals take for themselves **2** [*¹forage*] : the act of foraging : search for provisions ⟨they skirt the land like scouts upon a ~ —Eileen Duggan⟩

²for-age \'' *esp in pres part* -ējiŋ\ *vb* -ED/-ING/-S [ME *foragen*, fr. MF *fourager*, fr. *fourage*] *vt* **1 a** : to strip of provisions : collect forage from **b** *archaic* : SPOIL, PLUNDER **2** : to supply (as horses and cattle) with forage **3** : to secure by foraging ⟨*foraged* a chicken for the feast⟩ ~ *vi* **1** : to wander or rove in search of forage or food **2** : to secure forage (as for horses and cattle) by stripping the country **3** : RAVAGE, RAID **4** : to make a search : RUMMAGE ⟨*foraging* in his pockets for a match⟩ ⟨went *foraging* for bedroom slippers, shaving mirrors, and stationery —Bill Davidson⟩

³for-age \'fȯrij\ *n* -S [by folk etymology] : FORE EDGE (~ painting in bookbinding)

forage acre *n* : a unit of grazing value equivalent to one acre of land entirely covered with herbage that can be completely utilized by grazing animals — abbr. *F.A.*

forage cap *n* : a small military cap with a visor and a round flat crown to be worn with undress uniforms

forage density *n* : the proportion of the soil surface in a range or pasture that is covered by vegetation within the reach of animals

forage fish *n* : fish of value as food for other fishes more useful to man — compare FOOD FISH, GAME FISH, ROUGH FISH

forage grass *n* : grass used as feed for stock

forage harvester *n* : FIELD CHOPPER

forage poisoning *n* : staggers of domestic animals and birds due to toxic elements taken in with the food; *often* : BOTULISM

forage press *n* : BALER

for-ag-er \'fȯrəjə(r), 'fär-, -rēj-\ *n* -S [ME, fr. MF *fourageur*, fr. *fourager* + *-eur* -OR] **1** : one that forages **2** *foragers pl* **a** : soldiers detailed to forage **b** : cavalrymen advancing in line with extended intervals **3** : FORAGING ANT

forag-ing ant *n* : an ant (as the driver and army ant) that goes out in search of food in companies

for-a-lite \'fȯrəˌlīt\ *n* -S [L *forare* + E *-lite*] : a marking found in stratified rocks that resembles a worm's burrow

for-am \'fȯram\ *n* -S [NL *Foraminifera*] : one of the Foraminifera

fo-ra-men \fə'rāmən, fō'-\ *n, pl* **fo-ram-i-na** \-ramənə\ *or* **foramens** [L, fr. *forare* to bore, pierce — more at BORE] **1** : a small opening, perforation, or orifice : FENESTRA **2** [NL, fr. L] : MICROPYLE 2

foramen mag-num \-'magnəm\ *n* [NL, lit., great opening] : the large opening in the occipital bone through which the medulla oblongata passes to become the spinal cord

foramen of ma-gen-die \-məˌjhänˈdēē\ *usu cap M* [after François *Magendie* †1855 Fr. physiologist] : a passage through the midline of the roof of the fourth ventricle of the brain which together with the foramina of Key and Retzius affords a passage for the cerebrospinal fluid from the ventricles to the subarachnoid spaces

foramen of mon-ro \-mənˈrō\ *usu cap M* [after Alexander *Monro* †1817 Scot. anatomist] : the opening from each lateral ventricle into the third ventricle of the brain

foramen of wins-low \-'winzˌlō\ *usu cap W* [after Jakob B. *Winslow* †1760 Dan. anatomist] : EPIPLOIC FORAMEN

foramen ova-le \-ō'va(ˌ)lē, -'vā(-, -'vä(-\ *n* [NL, lit., oval opening] **1** : an opening in the septum between the two atria of the heart that is normally open only in the fetus **2** : an oval opening in the greater wing of the sphenoid for passage of the mandibular nerve

fo-ram-i-nal \fə'ramənᵊl\ *adj* [L *foramin-*, *foramen* + E *-al*] : of or occurring by way of a foramen (~ block)

foramina of key and ret-zi-us \-ˌkēən'retsēəs\ *usu cap K&R* [after Ernst A. H. *Key* †1901 and Gustaf M. *Retzius* †1919 Swed. anatomists] : passages at the lateral recesses of the fourth ventricle of the brain — see FORAMEN OF MAGENDIE

fo-ram-i-nate \fə'ramənˌāt\ *or* **fo-ram-i-nat-ed** \-ād-əd\ *adj* [L *foraminatus*, fr. L *foramin-*, *foramen* + *-atus* -ATE, -ATED] : having foramina : PERFORATED

for-a-min-i-fer \ˌfȯrəˈminəfə(r)\ *n* -S [NL *Foraminifera*] : one of the Foraminifera

fo-ram-i-nif-era \fəˌramə'nifə(ə)rə, ˌfȯrəmə'-\ *n pl* [NL, fr. L *foramin-*, *foramen* + NL *-i-* + *-fera* (fr. neut. pl. of L *-fer*)] **1** *cap* : an order of Rhizopoda comprising large chiefly marine protozoans that have one or more nuclei, that are generally enclosed in a typically calcareous shell having minute openings for slender branching pseudopodia and consisting of several successively formed communicating chambers each larger than the preceding, that have a complex life cycle in which sexual and asexual generations alternate, and that are so abundant that their shelly remains constitute a major part of various sedimentary limestones (as chalk) and serve to identify geologic horizons — compare INDEX FOSSIL; see BILOCULINA, GLOBIGERINA **2** : organisms belonging to Foraminifera

fo-ram-i-nif-er-al \ə'ramənˈifə(ə)rəl, ˌfȯrəmənˈifə(ə)rəl\ *adj* [NL *Foraminifera* + E *-al*] : of, derived from, or relating to the Foraminifera or their shells

¹fo-ram-i-nif-er-an \-rən\ *adj* [NL *Foraminifera* + E *-al*] : FORAMINIFERAL

²foraminiferan \''\ *n* -S : one of the Foraminifera

fo-ram-i-nif-er-ous \-rəs\ *adj* [NL *Foraminifera* + E *-ous*] : FORAMINIFERAL

fo-ram-i-nous \fə'ramənəs\ *adj* [L *foramin-*, *foramen* + E *-ous*] : having foramina : POROUS

fo-ram-i-nule \-məˌnyül\ *n* -S [L *foramin-*, *foramen* + E *-ule*] : a minute foramen

for and *conj, obs* : and also

for-as-much as \fȯrəzˌməch-, ˌfərəzˈm-\ *conj* [ME *for as much as*] : in consideration that : seeing that : SINCE ⟨*forasmuch as* the earth cannot hold aught beside them, you have dedicated the earth . . . to wisdom, liberty —F. L. Masters⟩ ⟨*forasmuch as* transatlantic firms are glad to print cheap popular translations —Caroline Ticknor⟩

for-as-te-ro \ˌfȯrəˈstē(ˌ)rō\ *n* -S [Sp, lit., stranger, fr. Catal *forastar*, *forestar*, fr. OCatal, fr. OProv *forestier*, fr. *forest* hamlet, country house, fr. (assumed) VL *forestis*, fr. L *foris* outside — more at FORUM] : any of various very productive cacaos with thick hard shells and purple seeds — compare CRIOLLO

¹for-ay \'fȯˌrā, -ə\ *also* 'fȯ-, *or* 'fō-, \ *vb* -ED/-ING/-S [ME *forrayen*, fr. MF *forrer*, fr. *forre*, *fuerre* fodder, straw — more at FORAGE] *vt*, *archaic* : to ravage in search of spoils : PILLAGE ⟨the night ~ our lands —Sir Walter Scott⟩ ~ *vi* : to make a raid or brief invasion ⟨*~ed* briefly into enemy territory⟩ : FORAGE, PILLAGE

²foray \''\ *n* -S [ME *farray*, fr. *forrayen*, v.] **1** : a sudden or irregular incursion for war or spoils : RAID ⟨abandoned its attacks against our principal ports except for attempted sneak and surprise ~s —D.D.Eisenhower⟩ : ATTACK ⟨these legislative ~s became tedious —*New Republic*⟩ **2** *obs* : spoils won in a foray : BOOTY

for aye *adv* [ME *for aye*] : ALWAYS, FOREVER, ETERNALLY

for-ay-er \-ə(r)\ *n* -S [ME *forrayer*, fr. *forrayen* + *-er*] **1** : one that makes or joins in a foray **2** *obs* : one that goes before : HARBINGER

forb \'fȯrb\ *n* -S [Gk *phorbē* fodder, food, fr. *pherbein* to graze, pasture; akin to OE *beorgan*, *birgan* to taste, eat, ON *bergja* to taste] : an herb other than grass : a broadleaf herb : WEED

forbade *or* **forbad** *past of* FORBID

¹for-bear \fȯr'be(ə)r, fər-, -'ba(ə)(ə)r; fōə'beə, fə'-, -'ba(ə)ə\ *vb* **for-bore** \-'bō(ə)r, -'bȯ(ə)r; -'bōə, -'bȯ(ə)\ *or archaic* **forbare** *pronounced like* FORBEAR\ **forborne** \-'bō(ə)rn; -'bȯ(ə)n\ **forbearing**; **forbears** [ME *forberen*, fr. OE *forberan* (akin to OHG *firberan* to refrain from, abstain, Goth *frabairan* to endure), fr. *for-* + *beran* to bear — more at FOR-, BEAR] *vt* **1** *obs* **a** : to bear with : ENDURE **b** : to control (feelings) **2** *obs* : to leave alone : SHUN ⟨~ his presence —Shak.⟩ **3** *obs* : to do without : endure the privation of ⟨fruits . . . whose taste too long *forborne* —John Milton⟩ **4** : to refrain from : abstain or desist from ⟨so poison-mean the marsh mosquitoes *forbore* to bite him —S.H.Adams⟩ ⟨could not ~ crying out⟩ ⟨wherever he has not the power to do or ~ any act —Frank Thilly⟩ : FORGO ⟨a merchant who could not ~ the fun of setting sail —*Times Lit. Supp.*⟩ ~ *vi* **1** : to hold back : ABSTAIN, DECLINE ⟨~, my friends, and spare me this ovation —W.S.Gilbert⟩ ⟨I cannot ~ from expressing my surprise⟩ **2** : to control oneself when provoked : be patient ⟨*forbore* with his friend's failings⟩ **syn** see FORGO, REFRAIN

²forbear *var of* FOREBEAR

for-bear-ance \-'berən(t)s, -'ba(ə)r-\ *n* -S [*¹forbear* + *-ance*] **1** : a delay in enforcing or a suspension of or a refraining from enforcing debts, rights of action, rights, privileges, claims, or obligations — compare RENEWAL **2** : the act of forbearing : the exercise of patience or restraint ⟨I believe you equal to every . . . domestic ~, so long as . . . you have an object —Jane Austen⟩ **3** : the quality of being forbearing : indulgence toward offenders or enemies : LONG-SUFFERING, LENIENCY ⟨known . . . for her ~ with her incorrigible husband —Willa Cather⟩ ⟨grateful for the help and ~ shown to us by the police —Basil Thomson⟩ ⟨~ has broadened into unconcern —Agnes Repplier⟩ **syn** see PATIENCE

for-bear-ant \-nt\ *adj* [*¹forbear* + *-ant*] *archaic* : FORBEARING ⟨equitable, nay ~ if need were —Thomas Carlyle⟩

for-bear-er \-rə(r)\ *n* -S : one that forbears

forbearing *adj* [ME *forbering*, fr. pres. part. of *forberen* to forbear — more at FORBEAR] : marked by calm patience esp. under provocation : slow to expression of resentment or acts of punishment or retaliation : PATIENT

syn TOLERANT, CLEMENT, LENIENT, MERCIFUL, INDULGENT: FORBEARING implies a calm unruffled abstention, esp. under provocation, from judging harshly or taking due action against something or somebody ⟨where life shall be seemly and noble and *forbearing* . . . yet strong enough withal to resist aggression —Learned Hand⟩ TOLERANT emphasizes the acceptance, often negative but usu. generous, of what one would be or

EXHIBIT 14

Merriam-Webster's Collegiate® Dictionary

ELEVENTH EDITION

Merriam-Webster, Incorporated
Springfield, Massachusetts, U.S.A.

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

Merriam-Webster™ is the name you should look for when you consider the purchase of dictionaries or other fine reference books. It carries the reputation of a company that has been publishing since 1831 and is your assurance of quality and authority.

Library of Congress Cataloging in Publication Data

Merriam-Webster's collegiate dictionary. — Eleventh ed.
p. cm.
Includes index.
ISBN-13: 978-0-87779-807-1 (Laminated unindexed : alk. paper)
ISBN-10: 0-87779-807-9 (Laminated unindexed : alk. paper)
ISBN-13: 978-0-87779-808-8 (Jacketed hardcover unindexed : alk. paper)
ISBN-10: 0-87779-808-7 (Jacketed hardcover unindexed : alk. paper)
ISBN-13: 978-0-87779-809-5 (Jacketed hardcover with CD-ROM : alk. paper)
ISBN-10: 0-87779-809-5 (Jacketed hardcover with CD-ROM : alk. paper)
ISBN-13: 978-0-87779-810-1 (Leatherlook with CD-ROM : alk. paper)
ISBN-10: 0-87779-810-9 (Leatherlook with CD-ROM : alk. paper)
ISBN-13: 978-0-87779-813-2 (Canadian)
ISBN-10: 0-87779-813-3 (Canadian)
ISBN-13: 978-0-87779-814-9 (International)
ISBN-10: 0-87779-814-1 (International)
1. English language—Dictionaries. I. Title: Collegiate dictionary. II. Merriam-Webster, Inc.
PE1628.M36 2003
423—dc21 2003003674
CIP

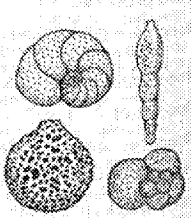
Merriam-Webster's Collegiate® Dictionary, Eleventh Edition, principal copyright 2003

COLLEGIATE is a registered trademark of Merriam-Webster, Incorporated

Made in the United States of America

9101112TT:QWV0807

-footer *n comb form* : one that is a specified number of feet in length, or breadth ⟨a six-*footer*⟩
foot-fall \'fůt-ˌfȯl\ *n* (1610) : the sound of a footstep
foot fault *n* (1886) : an infraction of the service rules (as in tennis, racquetball, or volleyball) that results from illegal placement of the server's feet — **foot-fault** \'fůt-ˌfȯlt\ *vi*
foot-gear \'fůt-ˌgir\ *n* (1837) : FOOTWEAR
foot-hill \-ˌhil\ *n* (1850) 1 : a hill at the foot of higher hills 2 *pl* : a hilly region at the base of a mountain range
foot-hold \-ˌhōld\ *n* (ca. 1609) 1 : a hold for the feet : FOOTING 2 : a position usable as a base for further advance
foot-ing \'fů-tiŋ\ *n* (14c) 1 : a stable position or placing of the feet 2 : a surface or its condition with respect to one walking or running on it; *esp* : the condition of a racetrack 3 : the act of moving on foot : STEP, TREAD 4 **a** : a place or position providing a base of operations : FOOTHOLD **b** : established position : STATUS; *esp* : position or rank in relation to others ⟨they all started off on an equal ~⟩ 5 : BASIS 6 : terms of social intercourse 7 : an enlargement at the lower end of a foundation wall, pier, or column to distribute the load 8 : the sum of a column of figures
foot-lam-bert \'fůt-ˌlam-bərt\ *n* (1925) : a unit of luminance equal to the luminance of a perfectly diffusing surface that emits or reflects one lumen per square foot
foo-tle \'fů-tᵊl\ *vi* **foo-tled; foo-tling** \-tᵊl-iŋ, 'fůt-liŋ\ [prob. alter. of *footer* to waste time] (1892) 1 : to talk or act foolishly 2 : to waste time : TRIFLE, FOOL — **footle** *n* — **foo-tler** \-tᵊl-ər, 'fůt-lər\ *n*
foot-less \'fůt-ləs\ *adj* (14c) 1 **a** : having no feet **b** : lacking foundation : UNSUBSTANTIAL 2 : STUPID, INEPT — **foot-less-ly** *adv* — **foot-less-ness** *n*
foot-lights \-ˌlīts\ *n pl* (ca. 1839) 1 : a row of lights set across the front of a stage floor 2 : the stage as a profession ⟨the lure of the ~⟩
foo-tling \'fů-tᵊl-iŋ, 'fůt-liŋ\ *adj* [*footle*] (ca. 1897) 1 : lacking judgment or ability : INEPT ⟨~ amateurs who understand nothing —E. K. Bentley⟩ 2 : lacking use or value : TRIVIAL ⟨~ matters⟩
foot-lock-er \'fůt-ˌlä-kər\ *n* (1942) : a small trunk designed to be placed at the foot of a bed (as in a barracks)
foot-loose \-ˌlüs\ *adj* (1873) : having no ties : free to move about
foot-man \-mən\ *n* (14c) 1 *archaic* : a traveler on foot : PEDESTRIAN **b** : INFANTRYMAN 2 **a** : a servant in livery formerly attending a rider or required to run in front of his master's carriage **b** : a servant who serves at table, tends the door, and runs errands
foot-mark \-ˌmärk\ *n* (1799) : FOOTPRINT
¹foot-note \-ˌnōt\ *n* (1607) 1 : a note of reference, explanation, or comment usu. placed below the text on a printed page 2 **a** : one that is a relatively subordinate or minor part (as of an event, work, or field) ⟨a movement now regarded as a ~ to architectural history⟩ **b** : COMMENTARY 3a
²footnote *vt* (1864) : to furnish with a footnote : ANNOTATE
foot-pace \'fůt-ˌpās\ *n* (1538) 1 : a walking pace 2 : PLATFORM, DAIS
¹foot-pad \-ˌpad\ *n* [*foot* + *pad* highwayman, prob. fr. *'pad*] (1678) : a criminal who robs pedestrians
²footpad *n* [*foot* + *'pad*] (1966) : a flattish foot on the leg of a spacecraft for distributing weight to minimize sinking into a surface
foot-path \'fůt-ˌpath, -ˌpäth\ *n* (1526) : a narrow path for pedestrians
foot–pound \-'paůnd\ *n, pl* **foot–pounds** (1850) : a unit of work equal to the work done by a force of one pound acting through a distance of one foot in the direction of the force
foot–pound–second *adj* (1892) : being or relating to a system of units based upon the foot as the unit of length, the pound as the unit of weight, and the second as the unit of time — abbr. *fps*
foot-print \'fůt-ˌprint\ *n* (1552) 1 : an impression of the foot on a surface 2 **a** : the area on a surface covered by something ⟨a tire with a wide ~⟩ ⟨the ~ of a laser beam⟩ **b** : range of operation (as of a service) ⟨a global ~⟩ 3 : a marked effect or impression ⟨left a ~ in the field of research⟩ 4 : something that identifies ⟨a genetic ~⟩
foot-race \-ˌrās\ *n* (1616) : a race run by humans on foot
foot-rest \-ˌrest\ *n* (1861) : a support for the feet
foot-rope \-ˌrōp\ *n* (1769) 1 : the part of a boltrope sewed to the lower edge of a sail 2 : a rope rigged below a yard for crew members to stand on
foot rot *n* (1708) 1 : a progressive inflammation of the feet of sheep, goats, or cattle that is associated with bacterial infection 2 : a plant disease marked by rot of the stem near the ground
foot-sie *or* **foot-sy** \'fůt-sē\ *n* [dim. of *'foot*] (1944) 1 : a furtive flirtatious caressing with the feet (as under a table) 2 : a usu. surreptitious cooperation or negotiation with someone supposed hostile to one's own interests — usu. used with *play*
foot-slog \'fůt-ˌsläg\ *vi* (1899) : to march or tramp through mud — **foot-slog-ger** *n*
foot soldier *n* (1622) 1 : INFANTRYMAN 2 : a person likened to an infantryman esp. in doing active and usu. unglamorous work in support of an organization or movement ⟨*foot soldiers* in the war against drugs⟩
foot-sore \'fůt-ˌsȯr\ *adj* (1719) : having sore or tender feet (as from much walking) — **foot-sore-ness** *n*
foot-step \-ˌstep\ *n* (13c) 1 : the mark of the foot : TRACK 2 **a** : TREAD **b** : distance covered by a step : PACE 3 : a step on which to ascend or descend 4 : a way of life, conduct, or action ⟨followed in his father's ~s⟩
foot-stone \-ˌstōn\ *n* (1724) : a stone placed at the foot of a grave
foot-stool \-ˌstůl\ *n* (1530) : a low stool used to support the feet
foot-wall \-ˌwȯl\ *n* (1860) 1 : the lower underlying wall of a vein, ore deposit, or coal seam in a mine 2 : the lower wall of an inclined fault
foot-way \-ˌwā\ *n* (15c) : a narrow way or path for pedestrians
foot-wear \-ˌwer\ *n* (1881) : wearing apparel (as shoes or boots) for the feet
foot-work \-ˌwərk\ *n* (1859) 1 : the activity of moving from place to place ⟨the investigation entailed a lot of ~⟩ 2 : the management of the feet (as in boxing); *also* : the work done with them 3 : active and adroit maneuvering to achieve an end ⟨fancy political ~⟩
¹foo-zle \'fů-zəl\ *n* (1890) : an act of foozling; *esp* : a bungling golf stroke
²foozle *vt* **foo-zled; foo-zling** \'fůz-liŋ, 'fů-zə-\ [perh. fr. G dial. *fuseln* to work carelessly] (1888) : to manage or play awkwardly : BUNGLE
¹fop \'fäp\ *n* [ME; akin to ME *fobben* to deceive, MHG *voppen*] (15c) 1 *obs* : a foolish or silly person 2 : a man who is devoted to or vain about his appearance or dress : COXCOMB, DANDY
²fop *vt* **fopped; fop-ping** (ca. 1590) *obs* : FOOL, DUPE
fop-pery \'fä-p(ə-)rē\ *n, pl* **-per-ies** (1546) 1 : foolish character or action : FOLLY 2 : the behavior or dress of a fop
fop-pish \'fä-pish\ *adj* (1599) 1 *obs* : FOOLISH, SILLY 2 **a** : characteristic of a fop ⟨a ~ dressing gown⟩ **b** : behaving or dressing in the manner of a fop — **fop-pish-ly** *adv* — **fop-pish-ness** *n*
¹for \(ˌ)fər, (ˌ)fȯr, *Southern also* (ˌ)fär\ *prep* [ME, fr. OE, akin to L *per* through, *prae* before, *pro* before, for, ahead, Gk *pro*, OE *faran* to go — more at FARE] (bef. 12c) 1 **a** — used as a function word to indicate purpose ⟨a grant ~ studying medicine⟩ **b** — used as a function word to indicate an intended goal ⟨left ~ home⟩ ⟨acted ~ the best⟩ **c** — used as a function word to indicate the object or recipient of a perception, desire, or activity ⟨now ~ a good rest⟩ ⟨run ~ your life⟩ ⟨an eye ~ a bargain⟩ 2 **a** : as being or constituting ⟨taken ~ a fool⟩ ⟨eggs ~ breakfast⟩ **b** — used as a function word to indicate an actual or implied enumeration or selection ⟨~ one thing, the price is too high⟩ 3 : because of ⟨can't sleep ~ the heat⟩ 4 — used as a function word to indicate suitability or fitness ⟨it is not ~ you to choose⟩ ⟨ready ~ action⟩ 5 **a** : in place of ⟨go to the store ~ me⟩ **b** (1) : on behalf of : REPRESENTING ⟨speaks ~ the court⟩ (2) : in favor of ⟨all ~ the plan⟩ 6 : in spite of — usu. used with *all* ⟨~ all his large size, he moves gracefully⟩ 7 : with respect to : CONCERNING ⟨a stickler ~ detail⟩ ⟨heavy ~ its size⟩ 8 **a** — used as a function word to indicate equivalence in exchange ⟨$10 ~ a hat⟩, equality in number or quantity ⟨point ~ point⟩, or correspondence or correlation ⟨~ every one that works, you'll find five that don't⟩ **b** — used as a function word to indicate number of attempts ⟨0 ~ 4⟩ 9 — used as a function word to indicate duration of time or extent of space ⟨gone ~ two days⟩ 10 : in honor of : AFTER ⟨named ~ her grandmother⟩
²for *conj* (13c) : for the reason that : on this ground : BECAUSE
³for *abbr* 1 foreign 2 forestry
FOR *abbr* free on rail
for- *prefix* [ME, fr. OE; akin to OHG *far-* for-, OE *fer*] 1 : so as to involve prohibition, exclusion, omission, failure, neglect, or refusal ⟨*for*bid⟩ 2 : destructively or detrimentally ⟨*for*do⟩ 3 : completely : excessively : to exhaustion : to pieces ⟨*for*spent⟩
fora *pl of* FORUM
¹for-age \'fȯr-ij, 'fär-\ *n* [ME, fr. AF, fr. *fuerre, foer* fodder, straw, of Gmc origin; akin to OHG *fuotar* food, fodder — more at FOOD] (14c) 1 : food for animals esp. when taken by browsing or grazing 2 [*forage*] : the act of foraging : search for provisions
²forage *vb* **for-aged; for-ag-ing** *vt* (15c) 1 : to strip of provisions : collect forage from 2 : to secure by foraging ⟨*foraged* a chicken for the feast⟩ ~ *vi* 1 : to wander in search of forage or food 2 : to secure forage (as for horses) by stripping the country 3 : RAVAGE, RAID 4 : to make a search : RUMMAGE — **for-ag-er** *n*
fo-ram \'fōr-am\ *n* (1927) : FORAMINIFER
fo-ra-men \fə-'rā-mən\ *n, pl* **fo-ram-i-na** \-'ra-mə-nə\ *or* **fo-ra-mens** \-'rā-mənz\ [L *foramin-, foramen*, fr. *forare* to bore — more at BORE] (1671) : a small opening, perforation, or orifice : FENESTRA — **fo-ram-i-nal** \fə-'ra-mə-nᵊl\ *or* **fo-ram-i-nous** \-mə-nəs\ *adj*
fo-ra-men mag-num \fə-ˌrā-mən-'mag-nəm\ *n* [NL, lit., large opening] (1857) : the opening in the skull through which the spinal cord passes to become the medulla oblongata
foramen ova-le \-ō-'va-lē, -'vä-, -'vā-\ *n* [NL, lit., oval opening] (ca. 1860) : an opening in the septum between the two atria of the heart that is normally present only in the fetus
fo-ra-mi-ni-fer \ˌfȯr-ə-'mi-nə-fər, ˌfär-\ *n* (ca. 1842) : any of an order (Foraminifera) of large chiefly marine rhizopod protozoans usu. having calcareous shells that often are perforated with minute holes for protrusion of slender pseudopodia and form the bulk of chalk and nummulitic limestone — **fo-ra-mi-nif-er-al** \fə-ˌra-mə-'ni-f(ə-)rəl; ˌfȯr-ə-mə-'ni-, ˌfär-\ *adj*
fo-ra-mi-nif-era \fə-ˌra-mə-'ni-f(ə-)rə; ˌfȯr-ə-mə-'ni-, ˌfär-\ *n pl* [NL, fr. L *foramin-, foramen* + *-fera*, neut. pl. of *-fer* -fer] (ca. 1836) : organisms that are foraminifers
fo-ra-mi-nif-er-an \-f(ə-)rən\ *n* (1920) : FORAMINIFER


foraminifer shells

for and *conj* (ca. 1529) *obs* : and also
for-as-much as \'fȯr-əz-ˌməch-'chaz\ *conj* (13c) : in view of the fact that
¹for-ay \'fȯr-ˌā, 'fär- *also* fə-'rā *or* fə-'\ *vb* [ME *forayen*, fr. AF *forreyer, forer*, prob. back-formation fr. **forrier, *forreour* forager, raider, fr. *fuerre, foer* provender — more at FORAGE] *vt* (14c) *archaic* : to ravage in search of spoils : PILLAGE ~ *vi* : to make a raid or brief invasion ⟨~ed into enemy territory⟩ — **for-ay-er** *n*
²foray *n* (14c) 1 : a sudden or irregular invasion or attack for war or spoils : RAID 2 : a brief excursion or attempt esp. outside one's accustomed sphere ⟨the novelist's ~ into nonfiction⟩
forb \'fȯrb\ *n* [Gk *phorbē* fodder, food, fr. *pherbein* to graze] (1924) : an herb other than grass
¹for-bear \fȯr-'ber, fər-\ *vb* **-bore** \-'bȯr\; **-borne** \-'bȯrn\; **-bear-ing** [ME *forberen*, fr. OE *forberan* to endure, do without, fr. *for-* + *beran* to bear] *vt* (bef. 12c) 1 *obs* : to do without 2 : to hold oneself back from esp. with an effort ⟨*forbore* mentioning the incident⟩ 3 *obs* : to leave alone : SHUN ⟨~ his presence —Shak.⟩ ~ *vi* 1 : HOLD BACK, ABSTAIN ⟨have *forborne* from taking part in any controversy —Abraham Lincoln⟩ 2 : to control oneself when provoked : be patient — **for-bear-er** *n*
²forbear *var of* FOREBEAR
for-bear-ance \fȯr-'ber-ən(t)s, fər-\ *n* (1576) 1 : a refraining from the enforcement of something (as a debt, right, or obligation) that is due 2 : the act of forbearing : PATIENCE 3 : the quality of being forbearing : LENIENCY
¹for-bid \fər-'id, fȯr-\ *vt* **-bade** \-'bad, -'bād\ *also* **-bad** \-'bad\; **-bid-den** \-'bi-dᵊn\; **-bid-ding** [ME *forbidden*, fr. OE *forbēodan*, fr. *for-* +